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Gold Treatment of Rheumatoid Arthritis

with some Notes on Hormone-Gold and Hormone-Salazopyrin Therapy

BY

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GOLD TREATMENT IN RHEUMATOID ARTHRITIS

WITH SOME NOTES ON HORMONE-GOLD AND HORMONE-SALAZOPYRIN THERAPY

BY

FOLKE BOHMAN

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PREFACE

The aim of the present investigation was to evaluate the prognosis of gold therapy in the treatment of rheumatoid arthritis and to compare the effects of such therapy with those produced by ordinary physical therapy. The long-term results as well as the immediate effects were considered.

The clinical material was composed of patients undergoing gold treatment at the Pensions Board's Hospital at Nynäshamn. A total of 502 gold-treated subjects from this hospital were studied. A control series comprised 362 patients who instead of being given gold had received routine physical therapy at other hospitals managed by the Pensions Board. The long-term results were evaluated on the basis of data derived from replies to a circularized questionary.

I am indebted in the first place to the Pensions Board for making available records concerning the patients treated and for coming to my aid when I had to procure further particulars about the patients. I am also grateful to the Board for various measures serving to facilitate the investigation.

To my chief, Doctor FREDRIK SUNDELIN, M.D., go my warm thanks for his constant interest in my investigation and all the help he so liberally gave me. Needless to say, his considerable experience of gold therapy has stood me in good stead.

For assistance with and advice about the statistical treatment of the data I turned to the State Institute of Human Genetics and Race Biology, Uppsala. I am glad to have this opportunity of thanking the chief of the Institute, Professor GUNNAR DAHLBERG, M.D., for his great help and sound advice not only with the statistical analysis but also with the planning of the investigation and the collection of the data. I also wish to put on record my indebtedness to the staff of the Institute, particularly Mrs. ELLA TIBBLING who gave valuable assistance in the statistical part of the work.

Professor NANNA SVARTZ, M.D., of the Caroline Institute and Caroline Hospital, Stockholm, had the courtesy to look over my results. She suggested that I should try some of the recently developed modes of treatment where hormones (cortisone and/or ACTH) are combined with other agents used in the control of rheumatoid arthritis. Appended to the work proper is accordingly a report on two series of cases: one treated with hormones combined with gold, and the other with hormones combined with Salazopyrin. However, as the patients available for this part of the study were few and could be observed only for a relatively

short period, I have refrained from drawing definite conclusions from the results obtained. It is my pleasant duty here to thank Professor SVARTZ for her advice, for valuable guidance concerning combination therapy with hormones and Salazopyrin and for the interest she has taken in my work.

I am indebted to the trustees of "Konung Gustaf V:s 80-årsfond" for grants to defray the costs of this investigation and to Astra Ltd. for material financial assistance.

CHAPTER 1

REVIEW OF THE LITERATURE

INTRODUCTION

Rheumatoid arthritis is a disease of unknown aetiology and incompletely known pathogenesis. It presents a variegated picture, and a substantial series of patients includes numerous variants which range from mild cases with insignificant symptoms to severe cases with general involvement of the extremital joints and general health. In addition, the course of the disease takes on a different aspect from one case to the next. Sometimes progress is slow with more or less marked exacerbations and remissions; sometimes total incapacity results after a short time only. It follows, clearly, that considerable difficulties accompany all attempts to assess the results of treatment in rheumatoid arthritis. The variability of the disease also makes it hard to assemble an adequate control series for a comparison with a series in which a particular kind of therapy has been used. And the varying course makes it difficult to tell what is *post hoc* and what is *propter hoc*. In order to assess adequately the effect of therapy in rheumatoid arthritis it would, accordingly, be desirable to base judgment on the following premises:

1. Complete data on the cases with as precise dates as possible for the beginning and end of treatment.
2. A compatible control series resembling the treated series as much as possible.
3. Full information about the follow-up period, viz. a description of the patients' status at the end of the course of treatment and after some years have lapsed. The follow-up should, of course, cover as long periods as possible.
4. In rheumatoid arthritis it is difficult to define improvement. Either the medical status or the working capacity can be used as the criterion. But the latter is to a large extent dependent on the patients' profession. With regard to the state of health one must at worst remain content with a general statement; but a report on the condition of the joints would clearly be preferable. The erythrocyte sedimentation rate, of course, provides significant information about the nature of the disease.

The primary aim of the present work was to assess the results of gold treatment for rheumatoid arthritis. The evaluation will be based on a comparison between gold treatment and other therapy, chiefly physical. Only seldom, of course, are all the premises mentioned above available when the effect of treatment is evaluated, and the relevant literature rarely meets these requirements. A purview of the literature, arranged in tabular form, will be given. First the results of gold therapy will be outlined, and then will follow other modes of treatment.

GOLD THERAPY

Gold treatment for rheumatoid arthritis has been used for about two decades and has grown increasingly popular in most countries. After some animal experiments regarding the action of gold in tuberculosis and other diseases, which chiefly were performed in Germany by FELDT (1913, 1926), LEWY & FREUND (1926) discovered that the gold drug "solganal" often was surprisingly beneficial in chronic streptomycoses. In 1927 LANDÉ and PICK presented the first reports on gold therapy in rheumatoid arthritis. The former had used "solganal" in 14 cases of infective arthritis, progress being halted in 9 cases; the latter had administered "triphal" in 2 cases of rheumatism with a chronic, afebrile course without achieving any results. In the period 1929–31 UMBER, ZIMMER, FELDT *et al.*, HEILBORN, FREUND, and others stressed the beneficial effects of gold treatment for rheumatic diseases, without, however, giving case reports. In 1930 FEHLOW, and in subsequent years ISRAELSKI, HUHN, UMBER and other German authors, published their results of gold therapy in rheumatoid arthritis. Gold treatment for rheumatoid arthritis was begun in France at about the same time as in Germany. FORESTIER (1929) was thus the first to report the results of treatment with "allochrysin". Since then he has published numerous papers on the subject and been responsible for many major advances. Since 1932 SECHER, a Dane, has published several papers containing reports of cases of rheumatoid arthritis treated with "sanochrysin". The first British investigation into the effects of gold in this disease was published in 1934 by SLOT & DEVILLE. Since then the subject has been dealt with by a number of British researchers (COPEMAN, TEGNER, HARTFALL, GARLAND, GOLDIE, etc.). Two short papers were published by American authors in 1936 (OREN, PHILLIPS), but U.S. physicians long took a critical attitude to gold therapy. In recent years gold therapy has nevertheless received increasing acclaim in the U.S.A., and reports have been published by many U.S. investigators. SUNDELIN is the Swede who has used gold therapy most frequently. He has, moreover, published the most comprehensive investigations into the side-effects of this therapy.

Results of gold therapy.

Tables 1a and 1b present the main investigations dealing with the effects of gold therapy in rheumatoid arthritis. Table 1a comprises investigations in which the results refer to the immediate response to therapy, or to the early response when not more than one year has elapsed after the end of therapy. It gives the name of the author, year of publication, number of cases, chief results, data on the gold drugs used, and, where such information was given, the total amount in g of each drug administered per course of treatment. Where several drugs were used and a total amount appears only after the last, the author administered the same dosage of all. If more than one dosage is given, the author concerned gave these amounts to different patients in his series. Table 1b is composed of investigations in which the patients were followed up. In addition to the data given in the preceding table, it provides information regarding the period of observation.

It stands to reason that these investigations not always can be compared. Some authors have appended to their own reports critical comments on others', pointing out incompatibilities that make comparison difficult (e.g. SASHIN *et al.*, 1939; SUNDELIN, 1941; BROWNING *et al.*, 1947; also SHORT & BAUER, 1948—cf. Table 5; KLING *et al.*, 1949; SNORRASON, 1950). In order to set up a more uniform and objective basis for evaluating disease activity, articular status and results of treatment in rheumatoid arthritis, some authors have suggested various systems (CECIL, 1937; TAYLOR, 1937; BAYLES & HALL, 1943; STEINBROCKER & BLAZER, 1946; STEINBROCKER, 1946; STEINBROCKER *et al.*, 1949). But rarely has any such system been adopted. Some authors have nevertheless described more or less fully the composition of the series studied and the implications of the terms used to denote results (e.g. HARTFALL *et al.*, 1937; TARSY, 1940; CECIL *et al.*, 1941; SUNDELIN, 1941; COHEN & DUBBS, 1943; COHEN *et al.*, 1945; L'ORANGE, 1945; RAGAN & TYSON, 1946; BROWNING *et al.*, 1947; BILLE, 1948; KLING *et al.*, 1949; SNORRASON, 1950; ADAMS & CECIL, 1950). But in many investigations the cases are incompletely described and the results inadequately defined.

As noted above it is naturally hard to tell whether in the separate case improvement is spontaneous or due to therapy. A control series is therefore a convenient aid to evaluation of the results. Unfortunately control series were used in only 14 of the 108 papers included in Tables 1a and 1b, most of the controls having been given physical therapy and the like. Some authors (ELLMAN & LAWRENCE, 1938; ELLMAN *et al.*, 1940; FRASER, 1945) have, however, compared cases given gold treatment with cases given some indifferent substance, but such series are small.

Obviously conclusions cannot be drawn from investigations in which only a few cases have been observed. Twenty-one of the investigations included in the tables comprised less than 25 cases (LANDÉ, 1927; PICK, 1927; FORESTIER, 1929; FEHLOW, 1930; ISRAELSKI, 1931; ADABACHE, 1931; HUHN, 1932; JACQ, 1933;

Table 1 a. Immediate results of gold treatment according to different authors.

Author	Year	Cases and controls (C)	Results (generally as expressed by authors) impr. = improved or improvement	Gold preparations (total amount in g per course)
Landé	1927	14	9 cases (65%) arrested	Solganal
Pick	1927	2	unimproved	Triphal
Forestier	1929	15	5 cases (33%) essentially impr., 5 cases (33%) impr.	Allochrysine (0.3)
Fehlow	1930	24	13 cases (55%) essentially impr.	Solganal (4–8)
Israelski	1931	12	4 cases (33%) impr.	Solganal (orally)
Adabache	1931	6	good results	Allochrysine (0.75)
Huhn	1932	22	62% cured, 24% essentially impr., 9% slightly impr.	Solganal B
Secher	1932	31	35% arrested, 45% essentially impr., 16% impr.	Sanocrysin (0.25 + 0.25 + 0.35 + 0.35, + 0.50 if reqd.)
id.	1933a	34	35% arrested, 47% essentially impr., 19% impr.	Sanocrysin
id.	1933b	46	28% arrested, 50% essentially impr., 20% impr.	Sanocrysin
id.	1933c	85	18% arrested, 41% essentially impr., 21% impr.	Sanocrysin
id.	1933d	103	17% arrested, 42% essentially impr., 25% impr.	Sanocrysin
Coste	1933	250	38%, 58%, 45%, 67% very good results; 57%, 71%, 65%, 72% good results	with Allochrysine, Crisalbine, Solganal B, Solganal B ol respectively
Fehlow	1933	150	40% almost cured	Solganal B ol (3–6)
Jacq	1933	7	good results	Allochrysine
Slot & Deville	1934	14	12 cases (85%) greatly impr.	Solganal A, Solganal B ol, Krysolgan
id.	»	17 C	worse results	
Bourderon	1934	153	71% good results	Allochrysine, Crisalbine, Solganal B, Solganal B ol (1.5–2.5)
Mester	1935	27	2 cases (7%) essentially impr., 4 cases (14%) moderately impr.	Allochrysine, Aurosan, Triphal
Umber *et al.*	1935	220	27% cured, 42% essentially impr., 31% slightly or not impr.	Aurodetoxin
Graber-Duvernay	1935	107	30–35% good results	Allochrysine, Crisalbine (1.5–1.8), Myoral
Secher	1935a	111	17% cured, 43% essentially impr., 25% impr.	Sanocrysin (0.25 + 0.25 + 0.35 + 0.50, + 0.65

Gripvall	1936	11	3 cases (27 %) cured, 5 cases (45 %) essentially impr.	Aurodetoxin (10–21)
Copeman	1936	2	almost cured	Allochrysine
McKenna	1936	25	100 % startlingly impr.	Myochrysine (2.2)
Guénon	1936	22	45 % essentially impr., 41 % impr.	Myoral (0.99)
Crosby	1936	27	33 % greatly impr., 41 % impr., 11 % slightly impr.	Allochrysine, Solganal B ol
Touw	1936	61	23 % very good, 36 % good, 36 % moderate results	Solganal B ol (3–3.5)
Bach	1936	>100	50 % responded well	Solganal B ol (2.5)
Slot	1936	12	9 cases (75 %) satisfactory impr.	Solganal, Oleosanocrysin (1.2)
Oren	1936	66	91 % responded well	Aurocein
Phillips	1936	9	2 cases (22 %) slightly impr.	Myochrysin (1.5)
van der Sleen	1937	72	75 % impr.	Solganal B ol
id.	»	59	66 % impr.	Myochrysine
Fronius	1937	102	16 % cured, 53 % greatly impr., 24 % impr.	Solganal B ol (3)
de Pap	1937	100	60 % very good results, 20 % impr.	Solganal B ol, Sanocrysin, Allochrysine (2)
Sashin & Spanbock	1937	22	12 cases (54 %) markedly impr., 5 cases (23 %) slightly impr.	Sanocrysine (0.75–2.15)
Snyder *et al.*	1937	100	45 % various degrees of impr.	Sanocrysine
Parr & Shipton	1937	70	8 % cured, 50 % greatly impr., 13 % slightly impr.	Myoral (2; 0.6)
Copeman & Tegner	1937	51	58 % greatly impr. or cured, 36 % impr.	Allochrysine (1–1.5)
Crowe	1937	60	50 % strikingly impr.	Solganal B ol
Secher	1938	263	59 % essentially impr., 33 % impr.	Sanocrysin
Hartfall *et al.*	1938	50	4 % cured, 84 % markedly impr., 6 % moderately impr., 2 % slightly impr.	Parmanil (0.6)
Raalte	1938	134	18 % very good, 34 % moderate results	Aurodetoxin (15–20)
Drukker & Plaat	1938	42	12 % cured, 36 % greatly impr., 36 % slightly or not impr.	Myochrysine (0.168)
Edström	1938	59	56 % arrested, 31 % impr.	Solganal A, Solganal B ol
Ellman & Lawrence	1938	16	50 % inactive, 44 % impr.	Solganal B (2.5)
id.	»	16	38 % inactive, 50 % impr.	Solganal B (smaller dosage)
id.	»	20 C	5 % inactive, 65 % impr.	
Key *et al.*	1939	53	6 % apparently cured, 34 % markedly impr., 8 % slightly impr.	Myochrysin (2)
Kempf	1939	19	58 % greatly impr., 37 % impr.	Neosolganal (2–3)

Table 1 a. Cont.

Author	Year	Cases and controls (C)	Results (generally as expressed by authors) impr. = improved or improvement	Gold preparations (total amount in g per course)
Kuipers	1939	200	30% very good, 43% good, 16% slight results	Solganal B ol (1; 2–3), Aurodetoxin
Snyder *et al.*	1939	50	2% excellent, 10% good, 36% fair results	Sanocrysine (0.99), Aurocein
Ellman *et al.*	1940	30	47% inactive, 47% impr.	Solganal B (2.5)
id.	»	30	27% inactive, 67% impr.	Solganal B (smaller dosage)
id.	»	30 C	3% inactive, 73% impr.	
Driscoll & Markson	1940	51	41% definitely impr.	Aurolsulfide (0.15–0.586)
Gardner	1941	250	70–80% impr.	Solganal B ol (1–1.2)
Tarsy	1941	36	53% markedly impr., 6% moderately impr., 11% slightly impr.	Gold colloid (1 metal)
Cecil *et al.*	1941	197	31% remission, 35% greatly impr., 19% moderately impr.	Myochrysin, Solganal B ol, Sanocrysine (1–2)
Bauer	1941	30	13% markedly impr.	Myochrysin, Solganal B ol (1–2)
Sundelin	1941	730	44% greatly impr., 49% impr.	Sanocrysin (1.06), Solganal (0.95), Neosolganal (3.7), Aurodetoxin (5.08), Myoral (0.89)
Thompson & Wyatt	1941	26	27% inactive or quiescent, 35% markedly impr.	Sanocrysine, Myochrysin (1)
Short	1942	31	19% subjective and objective impr.	Neosolganal, Myochrysin
Trauner	1942	5	100% cured	Neosolganal
Furlong	1942	16	56% markedly impr., 13% slightly impr.	Sanocrysine (1)
Robinson	1942	100	results in close correspondence with the European investigations	
Winkler	1943	32	47% good results, 44% fair results	Myochrysin, Chrysalbin (1), Solganal
Price & Leichtentritt	1943	101	59% definitely impr.	Myochrysin (1.2)
Snyder & Traeger	1943	28	4% apparently cured, 36% impr.	Aurolsulfide
Traut & Barton	1943	16	25% impr.	Sanocrysine (1), Sodium succinamid-aurate (0.25)
Ray	1943	50	50% definitely impr., 25% impr.	Calcium aurothiomalate
Graham & Fletcher	1943	95	16% remission, 51% very much impr., 20% impr.	Myochrysin (1)
Scholtz & Schubert	1943	50	no effect	Solganal (orally)
Cohen & Dubbs	1943	122	36% very much impr., 17% much impr., 35% subjectively impr.	Solganal B ol (1.24)

Douthwaite	1944	200	70% impr.	Myochrysin
Rawls *et al.*	1944	>100	25% markedly impr., 21% definitely impr., 12% slightly impr.	Solganal B ol
L'Orange	1945	234	83% impr.	Solganal B ol (1.2), Neosolganal (2–3)
Cohen *et al.*	1945	259	48% very markedly impr., 18% markedly impr., 22% impr.	Solganal B ol (1.2)
Halbertsma	1946	6	cured	Solganal B
Ragan & Tyson	1946	142	50% markedly impr., 39% definitely impr.	Myochrysin, Solganal B ol, Calcium aurothiomalate (0.5–4)
Short *et al.*	1946	35	20% moderately impr., 40% slightly impr.	Myochrysin (1)
Sundelin	1948	1904	90% subjective and objective impr.	Aurothion, Neosolganal, Solganal B ol, Sanocrysin, Aurodetoxin, Myoral (0.83 metal)
Bille	1948	43	58% greatly impr., 26% impr.	Neosolganal, Myoral, Aurothion, Sanocrysin (0.1–1 metal)
Kling *et al.*	1949	455	13% remission, 38% markedly impr., 37% moderately or slightly impr.	Sanocrysine (1–2)
id.	»	215 C	15% some degree of objective and subjective impr.	
Adams & Cecil	1950	106	66% remission, 23% greatly impr., 8% moderately impr.	Solganal B ol, Myochrysin (1–1.5)
id.	»	83C	24% remission, 33% greatly impr., 25% moderately impr.	
Egelius *et al.*	1951	210	78% impr.	(> 0.8 gold)
Cecil & Kammerer	1951	49	31% remission, 37% major impr., 12% minor impr.	Solganal B ol, Myochrysin (> 0.5)
id.	»	51 C	4% remission, 18% major impr., 12% minor impr.	

Table 1 b. **Follow-up results of gold treatment.**

Author	Year	Cases and controls (C)	Years of follow-up	Results (generally as expressed by authors) impr. = improved or improvement	Gold preparations (total amount in g per course)
Forestier	1932	48	<3	70% very good and good results	Allochrysine (1.5–2)
id.	1934	>500	2–3	70–80% responded well	Allochrysine (1.5–2), Solganal B (2.5–3), Myochrysine, Myoral
id.	1935	>550	2–3	70–80% responded well	Allochrysine (1.5–2), Solganal B (2.5–3), Myochrysine, Myoral
Pemberton	1935	69	0–5	17% cured, 40% very much impr., 32% impr.	Allochrysine (1.5–2), Crisalbine (1.5–3), Myochrysine (2)
Secher & Gudiksen*	1935	75	0–3	83% of 75 improved cases feeling well	Sanocrysin (0.25 + 0.25 + 0.35 + 0.35, + 0.65–0.75 if reqd.)
Hartfall *et al.*	1935	100	<2	10% apparently cured, 59% markedly impr., 23% slightly impr.	Crisalbine (2), Solganal B, Myocrisin
id.	1936	374	<3	8% apparently cured, 69% markedly impr., 15% slightly impr.	Crisalbine, Solganal B, Lopion
Forestier & Certonciny	1936	50	<3	64% very good results, 28% fair results	Sanocrysine, Solganal, Myochrysine, Allochrysine (1–2; 2–3.5)
Hartfall *et al.*	1937	690	<4	10% apparently cured, 57% markedly impr., 13% moderately impr.	Crisalbine, Myocrisin, Lopion, Solganal B ol (2; 1)
Sashin *et al.*	1939	80	½–5	44% very markedly impr., 39% moderately and slightly impr.	Sanocrysine (1), Aurocein
id.	»	120 C	»	15% impr.	
Edström	1939	129	½–2	81% able to work, 6% partially able to work	Solganal B ol (2–2.5)
id.	»	262 C	5–10	53% able to work, 11% partially able to work	
Tarsy	1940	22	¼–2½	55% greatly impr., 32% impr.	Myochrysin (2.2)
Dawson *et al.*	1941	100	½–2	22% inactive, 29% strikingly impr., 25% moderately impr.	Myochrysin (1), Solganal B ol
Wainwright & Brown	1941	68	½–2	44% markedly impr., 31% moderately impr.	Myochrysin (1)
Logefeil & Hoffman	1941	74	1–5	65% arrested or markedly impr.	Sanocrysine, Aurocein (1)
Cecil *et al.**	1941	197	½–5	25% remission, 25% greatly impr.	Myochrysin, Solganal B ol, Sanocrysine (1–2)
Smyth & Freyberg	1941	80	½–2	50% apparently cured or moderately or markedly impr.	Myochrysin, Sanocrysine (1)

				impr. cases)	
Hartung*	1943	264	>1	33% arrested	Myochrysin (1–2)
L'Orange*	1945	200	1½–3	13% cured, 56% impr. (28% able to work, 53% partially able to work)	Solganal B ol (1.2), Neosolganal (2–3)
Kalbak	1945	26	1–2	54% essentially impr., 42% impr.	Sanocrysin (2–4)
Fraser	1945	57	1	42% greatly impr., 21% moderately impr., 19% slightly impr.	Myocrisin (1)
id.	»	46 C	»	8% greatly impr., 13% moderately impr., 24% slightly impr.	
Ragan & Tyson*	1946	142	3–6½	13% remission, 43% impr.	Myochrysin, Solganal B ol, Calcium aurothiomalate (0.5–4)
Short *et al.**	1946	21	4–5	3% moderately impr., 20% slightly impr. of 21 impr. cases	Myochrysin (1)
id.	»	274 C	½–7	16% remission, 12% moderately impr., 25% slightly impr.	
Secher	1946	231	5–13	60–70% impr. or completely arrested	Sanocrysin (0.25 + 0.35 + 0.50 + 0.65 + + 0.75, + 0.75–1 if reqd.)
id.	»	99 C	»	4–5% arrested	
id.	1947	353	1–13	68% stopped, 14% essentially checked, 10% somewhat checked	Sanocrysin
id.	»	279 C	»	28% stopped, 21% essentially checked, 32% somewhat checked	
Browning *et al.*	1947	47	1½–6	23% impr.	Myochrysin (1–3)
Waine *et al.*	1947	58	3	21% arrested, 36% markedly impr., 24% impr.	Sanocrysine, Myochrysin (1.6 metal)
id.	»	62 C	»	10% arrested, 19% markedly impr., 27% impr.	
Kling *et al.**	1949	316	1–15	13% remission, 33% greatly impr., 47% some degree of impr.	Sanocrysine (1–2)
Snorrason	1950	295	4	80% arrested	Sanocrysin (by Secher)
id.	1950	169 C	4	50% arrested	
Adams & Cecil*	1950	106	1½–12	56% remission, 15% greatly impr., 17% moderately impr.	Solganal B ol, Myochrysin (1–1.5)
id.	»	83 C	»	36% remission, 14% greatly impr., 17% moderately impr.	

Table 1 b. Cont.

Author	Year	Cases and controls (C)	Years of follow-up	Results (generally as expressed by authors) impr. = improved or improvement	Gold preparations (total amount in g per course)
Egelius *et al.**	1951	210	5–15	15% cured, 30% impr.	> 0.8 gold
Cecil & Kammerer*	1951	28	1–10	80% remission or major impr. of 15 cases of rem. or maj. impr.	Solganal B ol, Myochrysin (> 0.5)
id.	»	20 C	»	71% remission or major impr. of 7 cases of rem. or maj. impr.	
Ekelund	1951	770	5–10	19% remission, 19% moderately impr., 17% slightly impr.	Only two thirds of the patients were gold-treated

* These writers also reported the therapeutical results immediately after completed treatment (cf. Table 1 a)

Slot & Deville, 1934; Gripvall, 1936; Copeman, 1936; Guénon, 1936; Slot, 1936; Phillips, 1936; Sashin & Spanbock, 1937; Kempf, 1939; Tarsy, 1940; Trauner, 1942; Furlong, 1942; Traut & Barton, 1943; Halbertsma, 1946), and these will be commented in exceptional circumstances only. Only 42 of the investigations included 100 cases or more, and 24 included between 50 and 99 cases.

Occasionally the results and numbers of patients specified are not exact, the authors having given approximate figures. This applies among others to Fehlow (1933), Forestier (1934, 1935), Bach (1936), Crowe (1937), Robinson (1942), Rawls *et al.* (1944). At the beginning of their papers some authors have stated that they treated a specified number of patients, but results are for various reasons not given for as many (e.g. Hartfall *et al.*, 1937; Cecil *et al.*, 1941; Graham & Fletcher, 1943; Short *et al.*, 1946). (The number of cases given in Tables 1a and 1b represents the number for which the author indicated results.)

It will be observed that the diagnoses are couched in terms varying slightly in different investigations. Early German authors often used the diagnosis "chronic infectious arthritis". Others have adopted more or less synonymous expressions, e.g. "primary chronic polyarthritis". Most British and American authors have adhered to the term "rheumatoid arthritis" or an equivalent.

Although some investigations have been concerned with various rheumatic diseases, it was usually possible to associate their cases of rheumatoid arthritis with the appropriate results. In his papers issued between 1932 and 1938 Secher, for example, used the diagnoses "polyarthritis chronica progressiva primaria" and "polyarthritis progressiva rheumatica", both of which probably are equivalent to rheumatoid arthritis (the two diagnoses quoted are given under the same heading in Tables 1a and 1b). In van der Sleen's (1937) study on various rheumatic affections, results are included for one group only, viz. "arthritis chronica multiplex infectiosa", and in Trauner's (1942) publication only for the 5 cases labelled "polyarthritis chronica primaria".

However, some authors have not classified their results in accordance with the different rheumatic diseases included in their studies. Spondylarthritis ankylopoetica, for example, is included in the studies made by Fehlow (1933), Mester (1935), Copeman & Tegner (1937), Sashin *et al.* (1939), Tarsy (1940), Winkler (1943), Ekelund (1951). Mester's (1935) series appears to have also included arthritides of tuberculous origin. Among the 220 patients studied by Umber *et al.* (1935), 10 per cent had diseases other than infectious arthritis and some of the arthritides were of acute type. Comprising 22 cases only, Guénon's (1936) investigations embraced different rheumatic diseases. Rheumatic fever was included in the study published by Scholtz & Schubert in 1943. A few cases of osteoarthritis were included amongst the cases observed by Snyder *et al.* (1937), Robinson (1942) and by Ray (1943).

Some of the series reported on in the literature were thus too heterogeneous to be of value in judging the results of gold therapy.

* * *

Table 2. Sex and age distribution and also duration and severity of rheumatoid arthritis in various authors' series.

Author	Year	Cases and controls (C)	Women %	Age at onset (O) of disease or beginning of treatment years	Duration years	Severity	
						Degrees	Remarks (class distribution)
Forestier	1932	48			40% < 2, 30% > 5		
id.	1934	500			20–30% < 2		
Forestier & Certonciny	1936	50	78	19–83	16% < 1, 42% > 5		
Copeman	1936	2		8, 14			
Touw	1936	61	72	most cases 30–70	19% < 1, 33% > 5		
Copeman & Tegner	1937	51	74	20–68	27% < 1, 37% > 5		
Hartfall *et al.*	1937	750	78	86% 20–60, 40% < 40 (O)	22% < 1, 43% > 5	7	2nd, 25%; 6th, 14%
id.	1938	50	72	40–60 (O)	30% < 1, 42% > 5		
Edström	1938	59		incl. some children			
Key *et al.*	1939	53		incl. 7 children			
Kuipers	1939	200	75		6 (average)		
Sashin *et al.*	1939	80	65	39.7 (mean)	5.4 (average)	selected severe cases	
Snyder *et al.*	1939	50		48% < 40, 32% 40–60	28% < 2, 72% > 2		
Tarsy	1940	22		25–66	1–18	4	2nd, 41%
Ellman *et al.*	1940	30		40 (O) (mean)	7 (average)		
id.	»	30		39 (O) (mean)	8 (average)		
id.	»	30 C		39 (O) (mean)	7 (average)		
Dawson *et al.*	1941	100			5 (average)		
Gardner	1941	250		12–81			
Logefeil & Hoffman	1941	74		most cases 30–60	11% < 1, 53% > 5		
Cecil *et al.*	1941	235	67	87% 20–60	28% < 1	4	2nd, 57%
Sundelin	1941	730	67	50% 21–40, 32% 41–50		3	2nd, 55%
Winkler	1943	32	66	16–65			
Price & Leichtentritt	1943	101	49	20–81, 55% > 50		3	2nd, 30%; 3rd, 57%
Cohen & Dubbs	1943	122		most cases 30–60	6% < 1, 46% > 5	4	3rd, most cases
Hartung	1943	264			most cases > 1		
L'Orange	1945	234	81	80% 20–60	13% < 1, 54% > 4	3	2nd, 56%; 3rd, 28%
Cohen *et al.*	1945	259				4	

id.	»	46 C)					
Halbertsma	1946	6		children			
Ragan & Tyson	1946	142	74	39 (O) (mean)	4 (average)		
Short *et al.*	1946	47	68	11–68	50% < 5	3	2nd, 66%
Browning *et al.*	1947	47	72		38% < 2		Yardstick by Bayles and Hall
Waine *et al.*	1947	58			5.5 (average)		
id.	»	62 C			4.4 (average)		
Bille	1948	43	71	< 1–15 (O)		3	2nd, 62%
Kling *et al.*	1949	455	72	60% > 40	7.5 (average)	3	2nd, 44%; 3rd, 52%
Snorrason	1950	352	83	17–76	½ 20	3	1st, 26%; 2nd, 60%
id.	»	205 C	88	»	»	3	1st, 29%; 2nd, 60%
Adams & Cecil	1950	106	67	40.7 (mean)	$\frac{1}{12}$ 1	all degrees	
id.	»	83 C	67	42.6 (mean)	»	»	»
Egelius *et al.*	1951	210	66	most cases 20–60 (O)	< 1 – 5	3	
Cecil & Kammerer	1951	49	50	≥ 60 (O)	55% – 1	4	1st, 43%; 2nd, 74%; 3rd, 10%
id.	»	51 C					

Although rheumatoid arthritis shows a predilection for women it affects men and children also, but its course in children seems to deviate in certain respects. Copeman's (1936), Halbertsma's (1946) and Bille's (1948) studies were exclusively concerned with children. Edström (1938) omitted to give particulars of his patients, though they did include some children; and the series of Key *et al.* (1939) comprised 53 subjects, of whom 7 were children. This study, however, was devoted to children only in passing.

The proportions of men and women in the various series are given in Table 2. It shows that in general the sex distribution was the same as that ordinarily obtained for rheumatoid arthritis, the average percentage of women being 70.7.

Obviously, if a pathological material is to be evaluated properly, it is most important to know the character of the cases in regard to the patient's age and the duration and severity of the disease. Often such data are sadly incomplete in the literature, but the most significant are also assembled in Table 2. Some authors' results, moreover, as appears in later section of this chapter, have been so associated with these three factors that various conclusions could be drawn about their material for study.

With regard to the effects of gold therapy it is important to distinguish between immediate and late results. Most authors have only concerned themselves with immediate or early results. Table 1a gives results up to a maximum of just under a year after the end of treatment. It will be seen that the short-term results were good in most cases. Yet some authors have had the opposite experience and have therefore taken a very critical attitude to gold therapy. Phillips (1936), Traut & Barton (1943) and Short *et al.* (1946) obtained poor results with gold. However, embracing as few as 9, 16 and 35, these studies should not be given overdue weight.

Some investigators have consolidated the results of preceding studies. Feldt & Beckstroem (1939), for example, in a synoptic article pointed out that gold has proved beneficial or curative in up to 80 per cent of rheumatoid arthritis series. Analyzing 7 studies with altogether 1537 gold-treated cases, Sashin *et al.* (1939) found that the average rate of cure or marked improvement was 54 per cent. In Cecil's (1940) opinion the results of gold therapy were on the whole similar in all countries and, irrespective of duration, about two-thirds of the cases benefitted greatly. Hench (1947) stated that the results of gold therapy for rheumatoid arthritis in more than 2000 cases in the U.S.A. and 1000 cases in other countries varied within wide limits, but on the whole 50–60 per cent had a remission or marked improvement.

In this connection it may be pointed out that some very experienced authors have made general statements about the prognosis following gold therapy. For example, having treated a thousand cases with gold, Hetherington (1937) asserted that it was the only agent capable of achieving revolutionary results. Forestier (1938) declared that gold therapy in rheumatoid arthritis led to recovery within a year of onset in 50 per cent of the cases, whereas a further

10–12 per cent were refractory to such treatment. Boots (1941), after several years' experience, said that only two-thirds of patients with rheumatoid arthritis can tolerate gold, 50 per cent of these being strikingly improved, i.e. 33 per cent of all cases.

The long-term results are, however, what really matter. About one third of the available papers on the results on gold therapy contain information about the follow-up period (Table 1b). Only 11 authors have published both immediate and late results. On the whole the long-term results seem quite favourable, but Short *et al.* (1946), Browning *et al.* (1947) and Ekelund (1951) were disappointed. A good many authors have not specified exactly the duration of the observation period. And many authors have followed up their patients for periods ranging from months to years. Clearly, however, it is not possible from such data to tell how long improvement has lasted in the separate case. And only a few authors have followed up their cases for more than 3 years (e.g. Forestier & Certonciny, 1936; Ragan & Tyson, 1946; Secher, 1946; Snorrason, 1950; Egelius *et al.*, 1951; Ekelund, 1951).

Relapses following gold therapy.

Improvements resulting from gold therapy have often been evanescent; after a varying length of time the disease has exacerbated. However, a difficulty arises out of the fact that most authors seem to have used the term "relapse" in either of two senses: (1) return of illness after apparent cessation of symptoms, or (2) aggravation after improvement without complete cessation of symptoms.

The relapsing rate has been stated in some investigations (see Table 3). Forestier & Certonciny (1936), for example, reported that 46 per cent of their patients had relapses during a follow-up period of at least 3 years. Hartfall *et al.* (1937) found "that relapse occurred in 129 of 613 cases (21 %), which had been seen within the past 3 months" and that "relapse was a common occurrence after the first (13.2 %) or subsequent (12.9 %) courses, but that a second relapse was a rarity. The relapse was most commonly seen about 6 weeks after the last injection of gold". Their cases were followed up for a period of at most 4 years. Sashin *et al.* (1939) observed relapses in 10.4 per cent of their cases after the first course. They had follow-up periods of 6 months to 5 years. Dawson *et al.* (1941) stated that relapses occurred in 12 per cent of 51 cases which had improved strikingly, the follow-up period ranging between 6 months and 2 years. Cecil *et al.* (1941) recorded relapses in 40 per cent of 68 cases in which there had been remission or great or moderate improvement. "A majority of the relapses occurred within a few weeks or few months after cessation of gold therapy." The cases had been followed up for 6 months to 5 years. Hartung (1943) reported relapses after at least 1 year in 21 per cent of those patients who had a remission. In the investigation published by Price & Leichtentritt (1943) 55 per cent of those patients who had shown initial improvement had a

Table 3. Relapses after gold treatment obtained by different authors.

Author	Year	Cases and controls (C)	Years of follow-up	Relapses in % of					Relapses in % after 1st course	Result of renewed treatment	Interval from treatment to relapse
				All cases	Cases of remission	Improvements					
						Marked	Moderate	Slight			
Forestier & Certonciny	1936	50	< 3	46						65 % good results	
Hartfall *et al.*	1937	613	< 4	21					13.2		6 weeks
id.	1938	50	< 1	12							
Sashin *et al.*	1939	80	½–5						10.4		
Dawson *et al.*	1941	100	½ 2			12					
Logefeil & Hoffman	1941	71	1 5						15.4		
Cecil *et al.*	1941	197	½ 5	35	34	50	33			23 % remission, 46% greatly and 12% moderately improved	weeks to months
Hartung	1943	264	> 1		21						
Price & Leichtentritt	1943	81	1 > 3			55				58 % improved	2-3 months
Ragan & Tyson	1946	142	1 1½	75						80 % »	
Short *et al.*	1946	21	1 5	37			86	50			
Browning *et al.*	1947	47	1 ½ 6	4							
Kling *et al.*	1949	116	5		57						
id.	»	32	10		75						
Adams & Cecil	1950	106	1 ½ 12		26	44					27 months (average)
id.	»	83 C	»		33	33					» »
Cecil & Kammerer	1951	28	1 10		33						
id.	»	20 C	»		29						

relapse after 1–3 years. The relapses commonly occurred 2–3 months after the last injection of gold. In a paper by Short *et al.* (1946) it is stated that within 4 to 5 years relapse had occurred in 13 of 21 improved cases, i.e. in 37 per cent of the series. Ragan & Tyson (1946) found that no fewer than 75 per cent of the patients had a relapse after 1–58 months. Among 116 patients who had a remission or great improvement after the first course of treatment, Kling *et al.* (1949) reported a relapse rate of 57 per cent within 5 years. Of 32 cases showing equivalent improvement which could be followed up for 10 years a relapse occurred in 75 per cent. The authors objected to this method of recording relapses, because most relapses were only partial and amenable to renewed gold treatment. Contending that the significant point was the duration of the relapse, they observed that the 116 patients with significant improvement after the first course spent an average of one year out of five in relapse, and those 32 who were followed up for 10 years spent three years out of ten in relapse. Snorrason (1950) claimed he could estimate the relapse rate, provided he knew the number of gold treatments given the patients. About 28 per cent of Snorrason's patients had undergone more than one course of gold treatment and about 21 per cent three courses. Adams & Cecil (1950) found that relapses occurred in 29 per cent of those patients who had a remission or great improvement after gold therapy, while 33 per cent of the corresponding controls had a relapse. The average period of observation for the gold-treated group was 47 months; for the controls 53 months. The average period of time from remission to relapse was the same for both groups—27 months. Cecil & Kammerer (1951) studied rheumatoid arthritis in persons over 60 years of age, during an observation period of 1–10 years, recording 5 relapses (33 per cent) in 15 patients who had attained an immediate remission or major improvement. Two of 7 patients of the same age who had not received gold treatment relapsed.

The relapse rate, as published in the literature, thus varies within wide limits. And the periods of observation have been highly different in the various studies. Sometimes, moreover, the relapse rate has been expressed in per cent of the total number of cases and sometimes as a proportion of those which were considerably improved, etc.

As a rule the relapses were not as severe as the original disease (Dawson *et al.*, 1941; Cecil *et al.*, 1941; Ragan & Tyson, 1946; Kling *et al.*, 1949; etc.). A majority of the relapses underwent improvement after a renewed course of gold therapy (Table 3), although the results were not as favourable then as after the first course. Some of the relapses were more or less refractory to treatment with gold, a factor particularly stressed by Fehlow (1933), Cecil *et al.* (1941) and Freyberg *et al.* (1942). To cite an example, Forestier & Certonciny (1936) stated that after gold therapy 65 per cent of their relapsed patients improved once again. Cecil *et al.* (1941) found that 23 per cent of the relapses had a remission, 46 per cent were greatly improved and 12 per cent moderately improved after renewed gold treatment. Ragan & Tyson (1946) reported that as many

as 80 per cent of the relapses showed improvement after a new course of gold treatment.

The erythrocyte sedimentation rate.

According to most authors the E.S.R. has proved most useful in rheumatoid arthritis for both diagnosis and prognosis. Studying the behaviour of the E.S.R. in rheumatic fever and rheumatoid arthritis, KAHLMETER (1926) found that it declined when rheumatoid arthritis improved clinically. Three years later he was able to report on the variations of the erythrocyte sedimentation rate in about 1000 cases of rheumatic disease. In two papers DAWSON *et al.* (1930) discussed the E.S.R. in about 200 patients with rheumatic affections. They partly found that it was a valuable adjunct in distinguishing between different rheumatic disorders—chiefly rheumatoid arthritis and osteoarthritis, partly that it was a sensitive indicator of the activity of rheumatoid arthritis and it could consequently be used to assess the efficacy of various modes of treatment. In ensuing years similar observations were reported by other authors (COSTE & FORESTIER, 1931; CECIL, 1933; RAWLS *et al.*, 1934; etc.).

However, it has also been found that the E.S.R. not always parallels the rheumatic process and even can be normal in active rheumatoid arthritis. FORESTIER & CERTONCINY (1936) stated, thus, that the E.S.R. was normal or subnormal in 10 per cent of their 50 cases. SASHIN *et al.* (1939) found a normal E.S.R. in but 1 of 80 selected cases of advanced rheumatoid arthritis. GOLDIE (1939) showed that prior to gold therapy the E.S.R. was 10 mm or less in 11 per cent of 400 cases. A normal E.S.R. occurred in 5 per cent of the 235 cases of CECIL *et al.* (1941), and the same was observed in 3 per cent of 259 cases by COHEN *et al.* (1945). FLETCHER & LEWIS-FANING (1945) reported an E.S.R. of 15 mm or more in 64 per cent of 228 cases of rheumatoid arthritis. The E.S.R. was normal in 3 per cent of the men and 10 per cent of the women patients studied by SNORRASON (1950). The same was true in 6.7 and 14.5 per cent of respectively 106 and 83 patients treated by ADAMS & CECIL (1950).

BACH (1947) maintained that in rheumatoid arthritis the E.S.R. should not be given undue weight. In a series of 50 cases he found some which exhibited clinical improvement associated with a raised E.S.R., and others where the E.S.R. declined without a corresponding clinical improvement. He further mentioned that FREYBERG had found an association between the clinical course and the E.S.R. in only 30 per cent of rheumatoid arthritis cases. Recently, however, other authors have started again to underline the significance of the E.S.R. for assessments of the activity of rheumatoid arthritis, e.g. STEINBROCKER, 1942; COMROE, 1944; COPEMAN, 1946; FLETCHER, 1947; STONE, 1947; and CYRIAX, 1947. Thus, although the E.S.R. can be normal in active rheumatoid arthritis and some authors consider it lacking in diagnostic significance, the majority of investigators seem agreed that it usually reflects the activity of the disease.

In connection with gold treatment for rheumatoid arthritis many authors have observed that clinical improvement often is accompanied by a marked fall of the E.S.R. (Fehlow, 1930; Secher, 1933c; Forestier 1935; Secher & Gudiksen, 1935; McKenna 1936; Guénon, 1936; Bach, 1936; Forestier, 1936; Forestier & Certonciny, 1936; van der Sleen, 1937; Sashin & Spanbock, 1937; Parr & Shipton, 1937; Copeman & Tegner, 1937; Hartfall *et al.*, 1937; Hartfall *et al.*, 1938; Edström, 1938; Ellman & Lawrence, 1938; Douthwaite, 1938; Goldie, 1939; Sashin *et al.*, 1939; Ellman *et al.*, 1940; Tarsy, 1940; Gardner, 1940; Wainwright & Brown, 1941; Sundelin, 1941; Logefeil & Hoffman, 1941; Cecil *et al.*, 1941; Smyth & Freyberg, 1941; Freyberg, 1942; Freyberg, *et al.*, 1942; Robinson 1942; Traut & Barton, 1943; Ray, 1943; Graham & Fletcher, 1943; Cohen & Dubbs, 1943; Hartung, 1943; Rawls *et al.*, 1944; L'Orange, 1945; Fraser, 1945; Cohen *et al.*, 1945; Short *et al.*, 1946; Sundelin, 1948; Snorrason, 1950).

Yet only a few authors have given figures for the E.S.R. changes during gold therapy. The most important of these data are collected in Table 4. The authors have given the one-hour reading (in mm, Westergren's Technique), except Goldie (1939) who gave half the sum of the one-hour reading and half the two-hour reading. As a rule the final E.S.R. was the reading taken immediately after the end of the gold therapy. However, in a few papers it was recorded also some time after the cessation of therapy (Dawson *et al.*, 1941; Snorrason, 1950). While most authors used the mean of the initial E.S.R. levels, the final reading is expressed in various ways—as a mean, as a percentage of normal, or as the decrease in mm (see Table 4).

Ellman & Lawrence (1938) and Ellman *et al.* (1940), for instance, showed that the E.S.R. returned to normal in 83 and 77 per cent of patients given large quantities of gold, in 43 and 37 per cent of those receiving small gold doses and in 26 and 13 per cent of the controls; but these authors studied small series only. In 33 per cent of 80 advanced cases of rheumatoid arthritis Sashin *et al.* (1939) reported that the E.S.R. became normal following gold therapy. One of their patients had a normal E.S.R. before treatment. Goldie (1939) demonstrated that the E.S.R. was normal (0–10 mm) in 41 per cent of 400 gold-treated patients, 11 per cent of whom had a normal E.S.R. prior to treatment. After gold therapy the E.S.R. was normal in 27 per cent of 100 of Dawson *et al.*'s (1941) patients, and in 28 per cent of these it still was normal 6 months to 2 years later. In 47 per cent of 130 markedly improved patients Cecil *et al.* (1941) found an E.S.R. which was normal or only slightly raised. Before gold treatment it was normal in 5 per cent of their patients. Being normal or almost normal in 43 per cent of Smyth & Freyberg's (1941) 80 gold-treated patients, the E.S.R. again rose some months later in 18 per cent of these subjects. L'Orange (1945) reported that the E.S.R. became normal in 41 per cent of 234 gold-treated cases. Snorrason (1950) observed a decline of the E.S.R. following sanocrysin therapy in 74 per cent of 55 male and 77 per cent of 278 female patients whereas the same was the case in 53 per cent of 25 male and 57 per cent of 124 female controls.

Table 4. E.S.R. after gold treatment according to different authors.
C = Controls F = Follow-up FC = Follow-up of controls

Author	Year	Cases or courses	Initial E.S.R. (mean)	Final E.S.R.				E.S.R. (mean) after course of treatment						
				Mean	Normal in % of: All cases	Normal in % of: Markedly improved cases	Diminished in % of all cases	1st	2nd	3rd	4th	5th	6th	7th
McKenna	1936	25 cases	41.8	10										
Copeman & Tegner	1937	51 cases					78*							
Edström	1938	59 cases			56	100								
Ellman & Lawrence	1938	16 cases			83									
id.	»	16 cases			43									
id. C	»	20 cases			26									
Sashin *et al.*	1939	80 cases	41.7	24.2	33									
Goldie	1939	400 cases	31.5		41	45		16.1	16.2	18.0	21.6	27.3	23.0	
Ellman *et al.*	1940	30 cases	25		77		93							
id.	»	30 cases	33		37		97							
id. C	»	30 cases	24		13		43							
Dawson *et al.*	1941	100 cases	44		27	41								
id. F	»	100 cases			28	41								
Logefeil & Hoffman	1941	74 cases					**							
Cecil *et al.*	1941	197 cases				47								
Smyth & Freyberg	1941	80 cases			43									
Sundelin	1941	1014 courses	34.7	26.6				26.6	25.1	29.6	26.3	34.6	32.0	36.0
Short	1942	31 cases			13									
Robinson	1942	>100 cases			95									
Graham & Fletcher	1943	95 cases	66					34						
L'Orange	1945	234 cases	68 % > 30		41		82							
Cohen *et al.*	1945	259 cases						8.1 %	7.3 %	14.3 %	normal E.S.R. of all cases			
Short *et al.*	1946	35 cases			17									
Sundelin	1948	2817 courses	36.8	24.6				21.5	25.8	30.6	29.4	30.7	29.9	25.3
Snorrason	1950	312 courses	43.2	30.1										
id. C	»	217 courses	41.4	43.7										
id. F (7 years)	»	272 cases		26.3										
id. FC (7 years)	»	48 cases		30.9										

* Average fall 38 mm for much improved cases, 8 mm for improved cases.

Some authors have, in addition, discussed changes in the E.S.R. following different courses of gold therapy. Goldie (1939), thus, demonstrated that from an initial level averaging 31.5 the E.S.R. dropped to 16.1 after the first, 16.2 after the second, 18.0 after the third and 21.6 after the fourth course. He emphasized that the decline was independent of the number of courses. Among 730 cases with 1095 courses, Sundelin (1941) found in 1014 of these courses that the mean E.S.R. declined 9.5 mm after the first, 6.4 after the second, 5.3 after the third and 8.3 mm after the fourth course, the average decrease for all courses (up to 7) being 8.1 mm. Seven years later the same author had studied 1904 additional cases which had received 2817 courses of gold treatment, and for these the corresponding E.S.R. declines were 15.1, 10.1, 8.2 and 7.5 mm, the mean for all courses (up to 7) being 12.2 mm. Cohen *et al.* (1945) showed that the E.S.R. became normal in 8.1, 7.3, and 14.3 per cent of the cases after 1, 2, and 3 courses respectively.

The fact that the E.S.R. not always varies in harmony with the clinical improvement has been pointed out by, among others, Secher & Gudiksen (1935), Parr & Shipton (1937), Hartfall *et al.* (1937), Snyder *et al.* (1939), Goldie (1939) and Cohen *et al.* (1945). They observed that the E.S.R. could rise even if the clinical results of gold treatment were very good. Goldie (1939) stated that while 16 per cent of markedly improved cases exhibited a raised E.S.R. it was decreased in 58 per cent of those cases in which there had been no clinical improvement. Cohen *et al.* (1945) reported that about 7 per cent of 259 patients showed clinical improvement following gold treatment, an increased E.S.R. notwithstanding.

The E.S.R. is sometimes found to go on declining even after the cessation of gold therapy, reaching normal levels weeks or months later (Fehlow, 1930, 1933; Secher, 1933c; Guénon, 1936; Copeman & Tegner, 1937; Ellman & Lawrence, 1938; Wainwright & Brown, 1941; Logefeil & Hoffman, 1941; Sundelin, 1948).

Some authors have pointed out that patients with active rheumatoid arthritis and normal E.S.R. respond clinically to gold therapy in a manner little, if at all, different from other cases. (Guénon, 1936; Cohen *et al.*, 1945; Snorrason, 1950). Parr & Shipton (1937) reported that cases of rheumatoid arthritis with a low E.S.R. prior to treatment responded even sooner than other cases.

In this connection it may be mentioned that some authors have stated that a raised E.S.R. was an early sign of impending relapse, since it often appeared long before clinical manifestations (Forestier, 1936; Bach, 1936; Secher, 1938). Goldie (1939) maintained that the E.S.R., even if raised in the majority of instances, remained constant in about one-third of the cases of relapse, and sometimes even declined. Therefore, Goldie added, the E.S.R. was valueless in predicting relapse.

To sum up, therefore, it seems that the E.S.R. is capable of deviating from the

clinical course of gold-treated rheumatoid arthritis; nevertheless most authors have made it clear that they consider it a valuable aid in evaluating the efficacy of gold treatment.

Age of the patient and duration and severity of the disease.

In connection with gold therapy for rheumatoid arthritis, attempts have also been made to ascertain the influence on the prognosis of such factors as the patient's age and the duration and severity of the disease. Only a few authors have had anything to say about the influence of age. Graham & Fletcher (1943) found that the mean age for the remissions was 33 years, for those who were very much improved it was 42 years, for the improved 37 years, and for the unimproved 49 years. The results were the direct response to gold therapy. Snorrason (1950) observed no appreciable effects of ageing on the results (up to 4 years after treatment). Egelius *et al.* (1951) stated that the age at onset seemed lower in those patients who were improved than in those who were worse when examined after 5 to 15 years.

Here it may be mentioned that varying opinions have been expressed with regard to the prognosis of rheumatoid arthritis at high age levels. Forestier & Certonciny (1936) said that rheumatoid arthritis took a relatively benign course in elderly patients. Schnell (1941), having examined 34 cases of rheumatoid arthritis in subjects over 55 years of age, stated: "the prognosis is much worse in the old than it is in the young." Cecil (1942) maintained: "rheumatoid arthritis seems to be more amenable to control when it develops later in life than when it develops in the third or fourth decade." Having studied the prognosis of rheumatoid arthritis in persons more than 60 years old, Cecil & Kammerer (1951) found that the immediate results of gold treatment compared favourably with those obtained by other investigators.

Many authors have shown that the prognosis is better if gold therapy is commenced early, and have consequently stressed the importance of early gold therapy in rheumatoid arthritis. (Secher, 1932–1938; Bourderon, 1934; Forestier, 1934; Forestier, 1935; Graber-Duvernay, 1935; Bach, 1936, Forestier & Certonciny, 1936; Copeman & Tegner, 1937; Hartfall *et al.*, 1937; Pap, 1937; Kuipers, 1939; Sashin *et al.*, 1939; Snyder *et al.*, 1939; Gardner, 1941; Cecil *et al.*, 1941; Graham & Fletcher, 1943; Cohen & Dubbs, 1943; L'Orange, 1945; Ragan, 1946; Adams & Cecil, 1950; Egelius *et al.*, 1951.)

Some of these investigators have mentioned a striking difference between the results in recent and old cases. Cecil *et al.* (1941), for example, observed that 78 per cent of those cases in which the disease had existed for less than one year had a remission or initially improved greatly after the gold therapy, whereas the corresponding figure for cases of longer standing was 62 per cent. At examination 1½–3 years after treatment, L'Orange (1945) demonstrated that improvement was inversely proportional to duration. The results were good in 92 per cent

of the cases where the disease had been present for less than one year, and in 42 per cent only when it was of more than 10 years' standing. Adams & Cecil (1950) found that improvement was far greater in patients who had received gold during the first 6 months after onset of the disease than in those started on gold therapy during the second half-year. Remission after treatment occurred in respectively 79 and 49 per cent of the two groups; whereas 12 and 38 per cent, respectively, were greatly improved. At follow-up examinations after $1\frac{1}{2}$–12 years, remission or great improvement was found in 77 and 62 per cent of the corresponding groups.

Others have found that the duration of the disease has no particular bearing on its prognosis. Thus, following up their patients for $\frac{1}{2}$–2 years, Dawson *et al.* (1941) stated that the mean duration at striking improvement was 4 years, at moderate improvement 6 years, at slight improvement 6 years, and at no improvement 4 years. Kling *et al.* (1949) reported a maximum of 56.6 per cent remissions and marked improvements in cases of 1–2 years' duration and a minimum of 47 per cent in cases of more than 5 years' duration; their observation period ranged between 1 and 15 years. Snorrason (1950) found that the duration of rheumatoid arthritis had no great effect on results 4 years after treatment.

Again others have emphasized that gold therapy produces striking results even when rheumatoid arthritis has been present for a considerable period, and have therefore considered it important to treat old-established cases also. (Forestier & Certonciny, 1936; Cohen & Dubbs, 1943; Kling *et al.*, 1949.)

In this connection it should be noted that some authors, mainly on account of the risk for complications, have considered gold therapy unjustified in recent cases. Hartung (1943) had two indications for gold therapy: a positive clinical diagnosis of active rheumatoid arthritis, and a duration longer than 3 months. He asserted: "one is not justified in using a form of treatment, which has at times serious toxic repercussions, unless the disease is well established and it is not likely to clear up spontaneously." Snyder & Traeger (1943), Comroe (1945) and Bach (1947) expressed the opinion that a trial should first be made with some form of therapy less dangerous than gold.

Some investigations have demonstrated that the severity of rheumatoid arthritis has a significant effect on the results of gold treatment. Sundelin (1941), for example, came to the conclusion that great improvement occurs in 56 per cent of mild cases, in 44 per cent of moderately severe cases, and in only 25 per cent of severe cases. Price & Leichtentritt (1943) stated that 93 per cent of mild, 80 per cent of moderate and 40 per cent of severe cases improved greatly following gold therapy. These two investigations were concerned with the primary results of treatment.

Other authors, however, have been unable to demonstrate any appreciable variations in the results which might be due to differences in severity. In his monograph on the erythrocyte sedimentation rate in 400 gold-treated cases of

rheumatoid arthritis, GOLDIE (1939) declared that the chances of improvement were equal in mild and severe cases as well as in cases with a high and a low initial E.S.R. CECIL *et al.* (1941) noted that 63 per cent of mild and 67 per cent of severe cases had an initial remission or great improvement after gold therapy. KLING *et al.* (1949) maintained that, at least in their patients, the severity of rheumatoid arthritis had no significant effect on the prognosis. They recorded a remission or marked improvement in 59 per cent of mild cases, 57 per cent of moderately severe cases and 46 per cent of severe cases: their follow-up period was 1–15 years. SNORRASON (1950) pointed out that after 4 years he found a percentage of arrested cases in the capsular stage which was only slightly higher than that in the osseous-capsular stage (91 and 83 per cent respectively).

To digress for a moment, it may be mentioned here that many a time one must of course expect the duration of the disease to be associated with its severity. Thus HARTFALL *et al.* (1937) in a large series of patients found that "there was a significant association between duration and disability; the disability steadily becoming worse as duration increased".

Furthermore, for the sake of completeness, it is interesting to note that in cases where rheumatoid arthritis is associated with psoriasis varying views have been held regarding the prognosis. Such cases which have been treated with gold preparations are discussed in publications published by FRASER (1945), RAGAN & TYSON (1946) and SNORRASON (1950). So, for example, RAGAN & TYSON (1946) reported poorer results of gold treatment in these (11 of 142) than in other cases. SNORRASON (1950) stated that gold therapy was about as effective in cases of associated rheumatoid arthritis and psoriasis (16 of 352 patients) as in cases of uncomplicated rheumatoid arthritis.

Gold preparations, dosage, No. of courses etc.

To produce maximal relief with minimal side-effects in rheumatoid arthritis which is treated with gold preparations, trials have been made with a variety of gold drugs, high and low dosages, many and few courses comprising different numbers of injections, etc.

Gold preparations[1] used in rheumatoid arthritis have in general been administered by the parenteral route. While trials have been made with administration *per os* (solganal), this form of treatment has played a minor part and been considered ineffective (ISRAELSKI, 1931; CECIL, 1941; SCHOLTZ & SCHUBERT, 1943). Among the large number of gold-containing drugs that have been developed for parenteral administration, the colloidal ones have proved least efficacious, but they have also been considered least toxic. TARSY (1941) stated

[1] The gold preparations used in the various investigations and the total amount of drug per course are given in Table 1. Being dealt with fully in numerous monographs, handbooks etc., the chemistry of the several drugs has been omitted here.

that, compared to other gold drugs, the effect of colloidal gold was neither as rapid nor as dramatic. According to Snyder & Traeger (1943), aurol sulphide was not as effective as the known common gold salts; but, on the other hand, Driscoll & Markson (1940) and Ray (1943) claimed comparatively good results with aurol sulphide and calcium aurothiomalate (which was part colloidal).

The gold salts most commonly used, the crystalloid ones, seem by and large to have been equally effective. Hartfall *et al.* (1937) remarked that crisalbine admittedly produced the largest number of "cures", but they pointed out that the chances of improvement proved equal for all the drugs administered in their large series of treatments. Sundelin (1941) obtained no statistically demonstrable differences between the 6 different gold drugs he had experimented with. Comparing a number of reports, Hartung (1943) confessed himself incapable of finding any differences in the actions of various gold preparations. Ragan & Tyson (1946) drew attention to the fact that the differences between the results obtained with their three gold preparations were not statistically significant. Hench (1947), reviewing various previous papers, pointed out that, while no particular gold preparation had any advantage over any others, some were less toxic than others and also less effective.

Gold treatment has generally been administered in the form of one or two weekly injections by the intramuscular or intravenous route, but dosages have varied widely. From 1932 to 1935 Forestier administered the gold drug in question, mostly allochrysine, in doses of 0.05–0.10 g per injection, giving 1.5–2.0 g per course of treatment. Next year, 1936, however, he increased the separate doses in some cases to 0.30 g and the total dosage per course to 3.5 g. He expected no definite changes in the condition until at least 2–3 months had elapsed after treatment (1932). Forestier & Certonciny (1936) stated that 70 per cent of those patients who had received a smaller dose of gold (altogether 1.5–2 g per course) improved greatly, while only 50 per cent of those on a larger dosage (altogether 2–3.5 per course) showed improvement of the same order. The latter patients had, however, a higher degree of disability.

Down the years Secher has on the whole kept intact his schedule of dosages, using large doses of sanocrysin. He maintained (1938) that, unlike many other investigators, he was not interested in the total dosage per course of treatment, instead—considering the storage and accumulation of gold in the system—he paid attention to the unit dose and any reactions that might occur. He pointed out (1935b) that his scheme's main advantage was its instant results, compared to Forestier's smaller doses which were effective only after a long period of therapy.

Though consistently fairly high, Sundelin's gold dosage levels have fluctuated somewhat over the years. He declared (1941) that during the period 1934–1940 he had altered the dosage of, for example, sanocrysin from 0.25–0.75 g first to 0.05–0.20 g and then to 0.10–0.50 g, the number of injections per course aver-

aging 9.7. Reporting on the cases given gold treatment during the past five years, he calculated (1948) that the amount of virgin gold given per course was 0.83 g, the average number of injections being nine. He went on to say that in order to achieve a rapid and adequate effect the dosage should be comparatively high.

On their large series of patients, HARTFALL *et al.* (1937) during the initial years used doses of the gold drug of 0.20 g, the total amount administered per course being up to 2 g, whereafter they decreased the dosage and gave up to 1 g per course. They observed that for those given in excess of 1.1 g of the drug the results were better than for those given less than this amount.

ELLMAN & LAWRENCE (1938) and ELLMAN *et al.* (1940) stated that for those patients who had received a total dose of 2.5 g of solganal B per course of treatment far better results were obtained than for those who had received a smaller dose.

In British and U.S. practice of recent years the unit dose of gold salt has generally ranged between 0.025 and 0.10 g, with a total dosage of 1–2 g per course of treatment. Yet even smaller doses have been given (FREYBERG *et al.*, 1942; RAWLS *et al.*, 1944; etc.). In the past few years British and American authors have found no significant differences between the results in cases given large and small doses of gold drugs. DAWSON *et al.* (1941) showed that the mean dose of gold preparation per course of treatment was 1.4 g in cases that were strikingly improved, while those which were slightly improved had received 2.0 g and the unimproved ones 1.5 g. LANSBURY (1943), while admitting that relief was slower and relapses more frequent than after large gold doses, was of the opinion that small doses produced as favourable results. RAWLS *et al.* (1944) emphasized that their results with small gold doses compared favourably with those obtained by others with larger doses. In a reviewing monograph HENCH (1947) stated that the dosage levels adopted of late in England and the U.S.A. had on the whole proved as effective as the larger doses used previously.

The importance of adjusting the gold dosage level to the individual needs of the patient and of administering the treatment in the form of repeated courses was realized at an early date already. In this respect gold treatment was copied on the lines of anti-syphilitic therapy (SECHER 1935b; FORESTIER, 1936; SLOT, 1936; EDSTRÖM, 1939; LANSBURY, 1943; etc.). For example, FORESTIER (1936) wrote that just as a symptomless but Wassermann-positive syphilitic should continue to receive treatment, so should an apparently cured case of rheumatoid arthritis with constantly raised E.S.R. continue to undergo gold therapy. One should not consider the pathological process in rheumatoid arthritis arrested, it was emphasized, until the E.S.R. had become normal and, if possible, the gold treatment should not be discontinued before then (FORESTIER, 1936; BACH 1936; etc.).

Many have recommended that a second course of gold treatment should be given 4–8 weeks after the first (FORESTIER, 1934; BACH, 1936; COPEMAN & TEG-

NER, 1937; KEY *et al.*, 1939; ELLMAN *et al.*, 1940; GARDNER, 1941; TARSY, 1941; CECIL *et al.*, 1941; COHEN & DUBBS, 1943; COHEN *et al.*, 1945 etc.). Others have advocated longer intervals—some months or longer—between courses (PRICE & LEICHTENTRITT, 1943; HARTUNG, 1943; FRASER, 1945; SUNDELIN, 1948; etc.). After the true course of gold therapy others again have continued to give gold in maintenance doses over prolonged periods. In the past few years this has been practised especially by FREYBERG *et al.* (1942), RAWLS *et al.* (1944), RAGAN & TYSON (1946), BROWNING *et al.* (1947), WAINE *et al.* (1947) and ADAMS & CECIL (1950). Some have apparently administered gold in repeated courses in order to consolidate results gained; others have delayed subsequent courses until signs of relapse have set in.

Some authors have published data about the results after different courses, a number having obtained better results after the second course than after the first. FORESTIER (1932) claimed the best results in those cases which had received several courses. COPEMAN & TEGNER (1937) recorded 45 per cent who were apparently cured or much improved, among patients given a single course, while the corresponding proportion was 72 per cent among those who had received more than one course. With respect to cures and marked improvements HARTFALL *et al.* (1937) reported 13 and 46 per cent respectively after the first course, 8 and 64 per cent after the second course and 4 and 80 per cent after the third. FREYBERG *et al.* (1942) had 55 per cent marked improvements after the first and 68 per cent after the second course; while COHEN & DUBBS (1943) obtained approximately the same results after the first and second course, namely 54 and 53 per cent marked improvements.

The frequent and often severe complications associated with gold therapy[1] have, of course, meant considerable drawbacks for this mode of therapy. Nevertheless it has often been observed that both mild side-effects and, chiefly, severe reactions sometimes can be accompanied by a dramatic improvement of the disease (SECHER, 1933 d, 1935 b, 1947; SLOT, 1936; CECIL, 1941; SUNDELIN, 1944, 1948; KALBAK, 1945; etc.). Thus SUNDELIN (1944) reported 14 cases, most of them of severe rheumatoid arthritis, in which the nature of the disease changed completely for the better after a complication had cleared up. He asserted (1948) that the improvement in cases with complications often was so rapid and miraculous that it could not but be associated with the complications.

PHYSICAL THERAPY

Physical therapy has long found a widespread use in rheumatoid arthritis. Even today this ailment is to a very great extent treated with various forms of

[1] Many authors of reports on gold therapy have also described the complications encountered. The largest work on this subject was published by SUNDELIN (1944) 730 cases and 1095 courses —who followed it up in 1948 with a further report on 1904 new cases and 2817 courses.

physical therapy, e.g. baths, local applications of heat, massage and rehabilitative exercise, electrotherapy, light and irradiation therapy, etc. Many authors have emphasized the value of physical treatment, but only a small number of comprehensive investigations have been published concerning the results of such therapy.

It has not been possible to relate the results of physical therapy to the course of the untreated disease, because truly untreated cases have not been available. There scarcely exists any patient with rheumatoid arthritis—and this has been pointed out time and again—who has not tried some form of medicamentous treatment or heat therapy, even if he has not consulted a doctor. It is known nevertheless that the natural course of rheumatoid arthritis is characterized by spontaneous remissions and relapses or exacerbations; that it occasionally progresses rapidly during a comparatively short period: and that it can remain stationary for years, etc. Many authors have shown this. Thus, in a study of relapse Ghrist & Hench (1929) gave an exposition of changes in course and prognosis. Ropes & Bauer (1945) accounted for 12 types of clinical manifestations in rheumatoid arthritis. Steinbrocker (1946) among other things described various characteristic patterns that the course of the disease may assume. Hench (1949) recounted the potential reversibility of rheumatoid arthritis and drew attention to a number of factors which affected it.

On the basis of experience some authors have attempted numerically to express the spontaneous course of the disease. One of them, Forestier (1936), claimed that spontaneous cures occurred in only 1–2 per cent of progressive rheumatoid arthritis cases, and that spontaneous remissions of more than one year's duration occurred in scarcely 10 per cent, data which often have been cited in the literature. Buckley (1936) stated that only in an occasional patient does rheumatoid arthritis become stationary or clear up without specific therapy, and that the disease leads to total disability in less than 10 per cent of the cases. He maintained, furthermore, that various therapeutic measures against rheumatoid arthritis lead to equivalent results on the whole. Dawson (1937) remarked that in a follow-up study of 140 untreated cases of rheumatoid arthritis Schneyer had found that 56 per cent of the patients were still capable of earning their own living after 14 years, while 22 per cent were unimproved. Dawson went on to say that after therapy 25 per cent were on the whole well, 50 per cent were improved and 25 per cent worse. Miller, cited by Tegner (1939), found that in his series of cases "70 per cent of chronic infectious arthritis receiving any or no treatment showed improvement, but this improvement takes as long as six years to appear, whereas with gold one can expect it in six months".

Thus, even if the main features of the spontaneous course of rheumatoid arthritis are known, naturally one cannot judge, when treating a case, how the disease would have developed had it gone untreated.

Table 5. Physical treatment for rheumatoid arthritis: results of important investigations.

F = Follow-up

Author	Year	Cases	Women %	Age at beginning (B) of disease or at admission to hospital, years	Years of follow-up	Results (generally as expressed by authors)
Cecil & Archer	1926	92				82% recovered or greatly improved of cases treated during first half year from onset of illness
Pemberton & Peirce	1927	77		10–75 (B)	≷10	22%, 100% improved; 34%, 75% improved; 21%, 50% improved; 14%, 25% improved
Kahlmeter	1927	203	68		2–5	54% entirely or to an essential degree able to work
id.	»	135	64		3–9	47% entirely or to an essential degree able to work
Alderin	1928	86	73	56%: < 40 (B)	3–4	49% entirely or to an essential degree able to work
Kuhns & Joplin	1936	452	67	Mean age males: 37, females: 38		50% able to work, 45% incapable of work, 5% dead
id. F	»	423			> 1	53% able to work, 29% incapable of work, 18% dead
Colver	1937	49	60	< 1–11		38% quiescent, 37% active, 25% death
Thompson *et al.*	1938	273	55	Mean age: 36.6 (B) Mean duration: 6.5 (B)		6% well, 36% markedly improved, 34% moderately improved, 11% slightly improved
id. F	»	103			1–6	87% of 87 cases of remissions, marked or moderate improvement unchanged or with continued improvement
Sclater	1943	388	75	49% : 35–54		16% disabled after 1 year's, 46% after 1-3 years' and 68% after 10 years' duration
Bohman	1944	1130	75	58%: 31–50	> 3	62% entirely or to an essential degree able to work, 10% partially able to work
Fletcher & Lewis-Faning	1945	253	81	Mean age males: 48.8, females: 47.8		23% free from symptoms, 41% improved
Holmdahl & Ingelmark	1946	278	74	51%: 30–50		80% improved working capacity after first course of treatment (91% after second course of treatment)
id. F.	»	224			⅔–3½	70% full or somewhat diminished working capacity, 14% moderately diminished working capacity
Short & Bauer	1948	250	63		½–16	15% remission, 17% moderately improved, 21% slightly improved

Results of physical therapy.

The most important investigations into the results of physical therapy are collected in Table 5. It gives authors, dates of publication, numbers of patients observed with their age and sex distribution, duration of follow-up periods, and results. The treatments given have assuredly varied considerably, but on the whole they can probably be classed as physical therapy of various types. But often other kinds of therapy have been given at the same time. Pemberton & Peirce (1927) thus, in addition, used tonics, protein and vaccine therapy and removal of infected foci. Thompson *et al.* (1938) in addition to physical measures used vaccine, blood transfusions, removal of infected foci, orthopoedic interventions, etc. when treating their patients. A minority of the patients in Bohman's (1944) series also received gold. Short & Bauer (1948) defined their schedule of treatment as simple medical and orthopoedic measures.

Sometimes the results have been related to the state of general health: sometimes to the capability of earning a living. Moreover a varying terminology has been used to define healthiness and working capacity. The observation periods have varied too. Consequently the several investigations can hardly be compared with one another.

The investigations performed by Kahlmeter (1927). Alderin (1928) and Bohman (1944) comprised respectively 338. 86 and 1130 patients who had received care at different times under the auspices of the Royal Swedish Pensions Board. Accordingly the series were fairly similar. Apart from a small proportion of Bohman's patients, who had received gold. general physical and medical treatment was on the whole given. Some years after the last period of treatment between 47 and 62 per cent of the patients proved fully or to a very great extent capable of earning their living.

Kuhns & Joplin (1936) found 53 per cent who were capable of working among 423 patients receiving convalescent care. Before then these subjects had been treated at hospital and only 15 per cent (66 of 452) were capable of working when admitted. The authors stated that their series also included cases of ankylosing spondylarthritis and Still's disease. the results being as good in Still's disease as in rheumatoid arthritis for elderly persons.

As noted (Table 1b) Edström (1939) studied the working capacity of patients receiving gold and of patients not receiving gold. Of the latter (262 cases) 53 per cent were fully fit and 11 per cent exhibited some degree of disablement 5–10 years after treatment. Also Holmdahl & Ingelmark (1946) evaluated their results with reference to the working capacity. After an average observation period of 1.2 years 70 per cent of 224 patients exhibited normal or slightly impaired working capacity, while it was moderately reduced in 14 per cent and seriously reduced in 16 per cent. When admitted to the first course of treatment 3.4 per cent were fit for work and 27.1 per cent completely disabled. Those patients who were able to work and those who were slightly disabled had to-

gether comprised 27.1 per cent; and the totally and seriously disabled patients had together comprised 34.7 per cent. During the first course of treatment the former group of 27.1 per cent of fully fit or slightly disabled patients increased to 62.7 per cent, while the proportion of completely or severely disabled declined from 34.7 to 12.7 per cent.

Other investigators give medical status. Their results reveal that remissions vary considerably. Following up 77 patients for more than 10 years PEMBERTON & PEIRCE (1927), for example, found that 22 per cent were in remission. THOMPSON *et al.* (1938) recorded remissions during treatment in 6 per cent of 273 cases, and it was found at a follow-up investigation 1–6 years later of 87 patients in whom remission or marked or moderate improvement had occurred following treatment that 87 per cent showed the same or a higher degree of improvement. FLETCHER & LEWIS-FANING (1945) observed a series of 253 patients, 23 per cent of whom had a remission. At follow-up examinations ½–16 years after treatment, SHORT & BAUER (1948) found that remission har occurred in 15 per cent of 250 cases, 38 of which, however, were rheumatoid spondylitis.

It can be mentioned that COLVER's (1937) follow-up study was performed on a series of 49 children with rheumatoid arthritis. He mainly discussed the treatment of focal lesions. At follow-up examination it appeared that the disease was quiescent in 38 per cent of the children and active in 37 per cent; 25 per cent had died. Complete recovery had occurred in about 1 out of every 4 cases, but only whenever the disease had become quiescent within 3 years. Deaths were most frequent during the first half of childhood.

Tables 1 a and 1 b show that some authors have compared their results of gold therapy with the events in a series of controls, most of whom were receiving physical therapy (SLOT & DEVILLE, 1934; SASHIN *et al.*, 1939; EDSTRÖM, 1939; SHORT *et al.*, 1946; KLING *et al.*, 1949; SNORRASON, 1950; CECIL *et al.*, 1950; CECIL & KAMMERER, 1951). Highly variable results have been obtained also in these investigations. SHORT *et al.* (1946), thus, recorded remissions in 16 per cent of 274 cases after a follow-up period of ½–7 years. ADAMS & CECIL (1950) did so in 36 per cent of 83 cases after 1½–12 years. After 4 years SNORRASON (1950) found that that 50 per cent of 169 cases had been arrested.

The erythrocyte sedimentation rate.

Some investigators have studied the relation between the E.S.R. and the results of physical therapy. FLETCHER & LEWIS-FANING (1945) stated: "it was found as regards infective arthritis that the chance of recovery or improvement was greatest among those patients whose E.S.R. was considerably reduced during treatment." While HOLMDAHL & INGELMARK (1946) were unable to find a statistically significant difference between the initial and final E.S.R. for the first course of treatment, they did show statistically that it very probably would diminish during home care following hospital treatment in those patients who

originally showed a level of over 40. Short & Bauer (1948) stated that in all cases attaining remission the E.S.R. (according to Rourke-Ernstene) was normal or only slightly elevated.

Here it may fittingly be mentioned that Tanberg (1937) examined the variations of the E.S.R. during balneotherapy for rheumatoid arthritis (664 courses). The cases were of varying duration and the initial E.S.R. reading ranged between normal levels and 120 mm. He discovered that it diminished in 65 per cent of the cases, increased in 27 per cent and remained unchanged in 8 per cent. Among patients with the initial E.S.R. lying between 16 and 50 a decrease occurred in 58–66 per cent, and decreases occurred in 70–90 per cent of cases in which it lay between 50 and 100. The author mentioned that the latter cases were not acute, the mean duration of the disease being about 3 years in patients with an E.S.R. over 60.

Age of the patient, and the duration and severity of the disease.

Some authors have demonstrated that the prognosis for physical therapy in rheumatoid arthritis is better in young than in elderly persons. Thus, in his first series of patients, Kahlmeter (1927) found at follow-up examination of those who had fallen ill before age 40 that 70 per cent of the men and 54 per cent of the women were fully or to a considerable extent capable of earning their living. Those who had fallen ill after age 40 showed poorer results: 61 per cent of the men and 37 per cent of the women showed similar degrees of fitness. In the second series, on the other hand, the results in the two age groups displayed no marked difference. The author reported, furthermore, that the age at beginning of treatment was an important factor for the prognosis. Respectively 80 and 77 per cent of those patients in the two series who were less than 20 years old were capable, fully or to a considerable extent, of earning their own living. But at higher age levels the results were less satisfactory. The same degree of fitness was thus found in but 44 and 53 per cent, respectively, among those patients who were more than 50 years old at the commencement of treatment. Alderin (1928) found no appreciable differences between the results at different age levels. At a follow-up examination 51 per cent of those who were younger and 46 per cent of those who were older than 40 years when they fell ill were wholly or almost wholly fit for work. Bohman's (1944) results were best for those who were between 21 and 30 years old at the beginning of treatment, 75 per cent of them being fit or very nearly fit for work when followed up. At higher age levels he obtained progressively poorer results, so that the same degree of improvement was recorded in only 40 per cent of those who came under treatment after 50 years of age. Holmdahl & Ingelmark (1946) reported improvement of the ability to work in 85 per cent of those patients who were younger than 40 years when they became ill and in 71 per cent of those who were older. Improvement occurred in 62 per cent of those of Short & Bauer's (1948) patients who were

less than 40 years old when treatment began. Of these 21 per cent had a remission. When they were over 40, only 42 per cent of the patients improved, 9 per cent of whom had a remission.

Most authors have reported better results of physical therapy in rheumatoid arthritis of short duration. Examining a series of 92 patients, CECIL & ARCHER (1926) obtained full recovery or great improvement in 82 per cent of those treated within 6 months of falling ill. Later, the percentage of good results declined progressively for each year the disease had existed. Seldom were patients whose symptoms had persisted for 5 years or more very markedly improved. KAHLMETER (1927), ALDERIN (1928) and BOHMAN (1944), found that longer duration was associated with poorer results. SCLATER (1943) classified 388 cases in four groups according to the severity of the disease, groups 3 and 4 comprising incapacitated cases. For durations of less than 1 year the incapacitated groups 3 and 4 included only 16 per cent of the cases. For durations of 1–3 years the incapacitated proportion had risen to 46 per cent, and for durations of more than 10 years it was 68 per cent. FLETCHER & LEWIS-FANING (1945) stated that in cases which had become symptomless the mean duration of the disease was 21.3 months, while it was 32.0 months in the improved and 38.7 months in the unimproved. HOLMDAHL & INGELMARK (1946) reported severe or moderate disablement at admission to hospital for the first course of treatment in 58 per cent of cases with less than one years' duration, in 77 per cent of cases with 1–2 years' duration, and in 78 per cent when the disease had existed even longer. At discharge from the first course the corresponding figures were 16, 41 and 45 per cent. STEINBROCKER (1946) mentioned that 90 per cent of 366 patients with acute rheumatoid polyarthritis were discharged as recovered within 3 months of admission for general medical treatment. He pointed out that the percentage of good results in subacute cases declined but was high nevertheless. SHORT & BAUER (1948) found that improvement occurred in 74 per cent of those patients who had been ill for a year or less (37 per cent remissions) while only 44 per cent improved of those who had been ill longer than a year (5 per cent remissions). They demonstrated, moreover, a marked difference between the results for various degrees of disablement. Improvement occurred in 80 per cent of cases designated "mild" with respect to total severity; but only 22 per cent of those in the group headed "marked total severity" showed improvement. In connection with gold therapy ADAMS & CECIL (1950) described a control series comprising 83 patients (see Table 1). Following up these patients, they found a remission or marked improvement in 60 per cent of those who were treated during the first 6 months after falling ill, but the same was true of only 39 per cent of those who were treated during the second period of 6 months.

Better results were observed in men than in women by KAHLMETER (1927) and SHORT & BAUER (1948). In KAHLMETER's (1927) first and second series, respectively, 66 and 57 per cent of the men and 48 and 42 per cent of the women displayed little or no disablement. After elimination of 38 cases of rheumatoid

spondylitis from Short & Bauer's (1948) series, it appears that improvement occurred in 69 per cent of the men, but only in 49 per cent of the women.

OTHER MODES OF TREATMENT

The aim of the present investigation is, as noted, to assess the effectiveness of gold treatment in rheumatoid arthritis. Generally speaking, the best way to estimate the efficacy of any given form of therapy is to compare sufficiently large numbers of treated and untreated cases. We have seen, however, that a large group of untreated cases of rheumatoid arthritis cannot readily be assembled. So the next best thing would be to have as a standard for comparison a series of rheumatoid arthritis cases that have been treated physically, alone or combined with any other therapy save gold. But, owing to the very nature of the disease, even this meets with difficulties where rheumatoid arthritis is concerned. For the course of rheumatoid arthritis is, as we know, characterized by fluctuations and from time to time shows more or less marked spontaneous remissions. Given a large enough series of cases, however, the effect of such spontaneous remissions will tend to cancel out statistically, so that a fairly exact picture can be formed of the true state of affairs.

For the sake of completeness we shall now review briefly some other forms of therapy for rheumatoid arthritis which have been said to be beneficial. But it will not be possible to compare them with gold therapy: partly the cases treated have been too few, partly not enough data are available about the patients.

Treatments involving the use of *metallic compounds* will be considered to begin with. Nyfeldt (1944), for instance, described 80 cases treated with Ebesal, a compound of copper, after which 28 per cent of his cases improved considerably and 49 per cent improved moderately. Other authors have had somewhat similar results with organic copper compounds: Forestier & Certonciny (1946), for example, observing great improvement in 42 per cent of 36 cases. Similarly, using manganese preparations, Brahme & Andersson (1941) reported very considerable improvement in 32 per cent and considerable improvement in 44 per cent of 200 patients. In a series of 80 ambulant patients correspondingly treated they observed very considerable improvement in 50 per cent and considerable improvement in 32 per cent. Obtaining very good or good results in half the cases, Douthwaite (1944), for instance, treated 12 cases of active rheumatoid arthritis with bismuth or bismuth salicylate, the observation period being 9 months to 1½ years. Fletcher (1947) stated he previously had treated a small series of cases with bismuth and obtained similar results. He had also used sodium bismuth tartrate, but could not estimate its effectiveness.

Many investigators have used *roentgen treatment*, which often is classified as physical therapy. Kahlmeter (1937), for example, stated that he had given

roentgen treatment in many thousands of cases of chronic arthritis, and he considered the results encouraging. He went on to say that numerical expressions for the results were of slight value because, depending on the stage and type of the disease, they varied widely. In a series of 100 cases, the majority of rheumatoid arthritis, SMYTH *et al.* (1940) obtained good results with roentgen therapy. Among SWAIM's (1940) series of 85 roentgen-treated cases of rheumatoid arthritis, 90 per cent of those of less than 6 months' duration improved while those of more than 2 years' duration improved subjectively in 72 per cent and objectively in 52 per cent of the cases. Other authors have found roentgen therapy to be of doubtful value or considered it a means capable of giving temporary improvement or suitable for use as last resort (HENCH *et al.* 1942; STEINBROCKER, 1942; COMROE, 1944; FLETCHER, 1947).

Just as for many other diseases, *focal infections* have been given a prominent place in the development of rheumatoid arthritis. Down the years, many theories based on focal infections have seen the light, and they have offered a variety of explanations of this relationship. Quite a few years ago, removal of infected foci consequently occupied a prominent position in the therapeutic armamentarium for combating rheumatoid arthritis. Removal of infected foci for rheumatoid arthritis is the subject of many publications, but only a few illustrate its effect with case reports. The latter are devoted chiefly to the results of tonsillectomy, whereby a few authors have achieved good results. LILLIE & LYONS (1919) recounted the results of tonsillectomy in 200 cases of which 28 were severe arthritides of which 56 per cent improved following the operation. The follow-up period was about one year. JANSEN (1920) stated that he had tonsillectomized a considerable number of cases and obtained good results in secondary forms of chronic polyarthritis. Having tonsillectomized 19 cases of rheumatoid arthritis, GORDING (1925) reported good results in 11 (59 %) after a follow-up period of 1–1½ years. HOLBROOK (1933) found that removal of infected foci proved of value for the subacute and early chronic cases in a series of 100 patients with chronic atrophic arthritis. After removing infected foci in 198 of 343 cases, THOMPSON *et al.* (1938) obtained a higher proportion of improvements (82 %) among the 198 cases than among the rest.

Other authors have been doubtful about the effect of focal removal in rheumatoid arthritis. PEMBERTON & ROBERTSON (1920) found in a series of 400 cases of arthritis—under which heading, however, they grouped a variety of affections—that 16 per cent were improved by removal of foci, but that 46 per cent recovered in the presence of demonstrable surgical foci. JARLØV & KRAGH (1931) demonstrated improvement in 9 of 17 (53 per cent) tonsillectomized cases while 37 cases of 72 (53 %) which had not been tonsillectomized improved after some years' observation. In their opinion tonsillectomy had no significant effect. Among BURBANK & CHRISTENSEN's (1931) 465 tonsillectomized and vaccinated cases about 60 per cent were unimproved or worse and about 40 per cent markedly improved

or symptomless. Cecil & Angevine (1938) stated that temporary improvement occurred in 7 of 27 tonsillectomized cases.

On the whole finding it of probable value, some authors have, without reporting any treated cases, expressed their opinions about removal of infected foci in rheumatoid arthritis. (Cecil, 1934; Ravenna, 1940; Short & Bauer, 1942; Hench *et al.*, 1942; Comroe, 1944; etc.) Dahlberg *et al.* (1950) compared 335 tonsillectomized cases of rheumatoid arthritis with 267 non-tonsillectomized, and "no statistically significant or probable difference was obtained in regard to the sedimentation rate on admission or on discharge between the operated and non-operated cases".

Most authors in recent years seem to hold the opinion that removal of infected foci is of significance for the general state of health, but has no specific action on the rheumatic disease.

A variety of *vaccines* have found widespread use, particularly in the 1930's. Some authors have considered vaccinotherapy encouraging and emphasized that good effects can be obtained in certain cases of rheumatoid arthritis (Cecil *et al.*, 1929; Holbrook, 1933; Cecil, 1934; Haden, 1937; Bach, 1947; etc.). Others have been more enthusiastic. For instance, Crowe (1930) claimed successful results in from 50 to 90 per cent of all cases of rheumatic diseases; and in 1937 he reported favourable results in 85 per cent of a series of 5000 cases after vaccinotherapy. His series included osteoarthritis however. Coste & Lacapère (1931) obtained recovery in 19 per cent and improvement in 57 per cent of 67 cases of chronic polyarthritis which had been treated with cuti-vaccine. Burbank & Christensen (1931) treated 1016 cases of chronic arthritis with specific vaccine. Of these 17 per cent became symptomless and 57 per cent improved very markedly. In conjunction with other therapy, Wetherby (1941) gave vaccine to some and saline solution to others in a series of 80 patients with rheumatoid arthritis, clinical improvement occurring in 83 per cent of the former but only in 40 per cent of the latter.

Again other authors have doubted the value of vaccinotherapy (Dawson & Boots, 1933; Kovacs, 1936; Jordan, 1937; Short & Bauer, 1942; Comroe, 1944; etc.). To take an example among these, it may be mentioned that Kovacs (1936) found in 57 cases of rheumatoid arthritis treated with three different kinds of vaccine an improvement rate between 33 and 42 per cent.

Often given in the form of typhoid vaccine, *foreign protein therapy* has been said by most authors to produce a temporary improvement of some weeks' duration, or perhaps longer in a minority of cases (Hench *et al.*, 1942; Steinbrocker, 1942; Comroe, 1944; Bach, 1947). Other authors' opinion had been that this mode of treatment is absolutely worthless or even detrimental (Cecil, 1934; Fletcher, 1947; etc.). In recent years this form of therapy has probably been less popular than formerly.

Similar opinions have been voiced about *fever therapy*. Such therapy has, thus, been said to produce either transient amelioration of the symptoms, or no effect

whatsoever (Cecil, 1934; Short & Bauer, 1935; Hench & Slocumb, 1935; Cecil, 1941; Hench *et al.* 1942; Steinbrocker, 1942; Comroe, 1944; Bach, 1947). For example, Short & Bauer (1935) after fever therapy (diathermy) in 25 cases of rheumatoid arthritis obtained 80 per cent immediate improvements, which in only 20 per cent of the cases persisted for 6–41 months. Among 60 fever-treated cases ("Hypertherm") Hench & Slocumb (1935) observed 17 per cent with marked and 46 per cent with moderate improvements following therapy, but 8–11 months later 18 per cent with marked and 20 per cent with moderate improvements.

Sulphur has also had a significant place in therapy for rheumatoid arthritis. According to some authors, aberrations of sulphur metabolism characterize rheumatoid arthritis, and that is why they advocate sulphur therapy. For instance, Rawls *et al.* (1935) treated 100 cases (some osteoarthritis) with colloidal sulphur and recorded improvement in 60 per cent of those patients whose ungual cystin content they considered low, whereas only 24 per cent of the remainder improved. Woldenberg (1937) examined 356 patients receiving colloidal sulphur and found this mode of therapy very valuable. He stated that 78 per cent were relieved of pains after a few injections, that hydrops resolved after some weeks, etc. Nevertheless a number of authors stated in 1939 (Freyberg *et al.*, Key, Margolis, Pilot, Senturia, Comroe, Bauer) that there was no difference of significance between the excretion of sulphur in patients with rheumatoid arthritis and that in normals, and that there consequently existed neither a metabolic nor a biochemical indication for sulphur therapy. They found, on the contrary, that sulphur had an unspecific action. Among these authors, Bauer (1939) emphasized that Abrams in 50 per cent of 14 cases observed subjective improvement which, however, in no case persisted for more than 3 months. Short & Bauer (1942) and Comroe (1944) considered sulphur therapy of questionable value. Bach (1947) stated: "colloidal sulphur is no longer a recognized form of therapy for rheumatoid arthritis."

The use of *bee venom* against rheumatoid arthritis is based upon the supposed immunity to this disease among bee-keepers. Kroner *et al.* (1938) after giving apicosan (bee venom) obtained marked improvement among 35 of 100 patients with rheumatoid arthritis. Having treated 27 cases of rheumatoid arthritis with the sting of the honey-bee, Nicholls (1938) obtained marked improvement in three. He considered the results disappointing. In the opinion of Hench *et al.* (1942) and Short & Bauer (1942), bee-venom therapy is a measure of questionable value.

In rheumatoid arthritis therapy trials have also been made with *cobra venom*, but it has merely produced transient pain-relief. Steinbrocker *et al.* (1940) and Talkow & Bauer (1943), respectively, reported 14 and 12 cases of rheumatoid arthritis which had been treated thus. They observed an analgesic action in a small number of cases.

The place of *vitamins* in rheumatoid arthritis has been the subject of a vigorous

debate. Some authors have stressed the fact that signs of avitaminosis have been observed more frequently in rheumatoid arthritis sufferers than in normals. Some investigations have shown that rheumatoid arthritis is associated with a depressed vitamin-C level in plasma. RINEHART *et al.* (1938) found this to be the case in 26 cases, and concluded that vitamin-C deficiency is a significant factor in the aetiology of rheumatoid arthritis. In contradistinction to this, other authors have stated that C-avitaminosis is also a frequent sign in other chronic diseases.

Some investigators have experimented with massive vitamin-D doses in rheumatoid arthritis. One team, WYATT *et al.* (1936), reported clinical improvement in 20 per cent of 40 cases following such therapy. ABRAMS & BAUER (1938) obtained subjective improvement in 5 of 18 cases and both subjective and objective improvement in 3 of the remaining cases. HENCH *et al.* (1938) were unable to find a remission among 25 patients, but some of them showed a measure of subjective improvement. Treating 23 cases with Ertron, a vitamin D preparation, SNYDER & SQUIRES (1941) obtained excellent results in 7 cases and good in 6 after one years' follow-up.

Integrating the results of other authors' investigations with his own experiences, FREYBERG (1942) stated that many had achieved adequate compensation for existing vitamin deficiencies by administering large doses of vitamins A, B and C, and that temporary improvement was produced occasionally by large doses of vitamin D. He emphasized that there existed no anti-rheumatic vitamin. In summing up, COMROE (1944) also asserted that there is no evidence to show that the disease develops as a result of a particular vitamin deficiency.

Obviously various antibiotics and sulpha drugs have been tried in the control of rheumatoid arthritis—usually without avail. However, it is very interesting here to consider SVARTZ's (1941) report on experiments with a new sulpha drug. For several years she had been using simultaneous administration of sulpha and salicylates in the treatment of rheumatic polyarthritis: and also a chemical compound of these two drugs types, but had no appreciable success. Then (1941), in collaboration with Messrs. Pharmacia Ltd. Drug Manufacturers, she produced the substance salicyl-azo-sulphapyridine which was given the brand name of *Salazopyrin*. It proved effective in certain cases of rheumatic polyarthritis. Later the same year SVARTZ published the results of Salazopyrin administration in the treatment in some cases. The results were most favourable "in fresh cases where the sedimentary blood reaction was high". In passing it may here be mentioned that Salazopyrin therapy was tried also in cases of ulcerative colitis, a disease where it subsequently gained widespread use. In 1942 SVARTZ reported good results of Salazopyrin treatment for rheumatic polyarthritis in 11 cases. In most of these cases the E.S.R. took a marked turn to the better. Two years later (1944) she reported that patients frequently acquire Salazopyrin resistance, and she had therefore started to give the drug over periods of 2 or 3 weeks alternating

with periods of liver and vitamin B therapy. She had also used artificial hyperthermia as an adjunct in Salazopyrin treatment. Some patients had shown marked improvement after such treatment. SVARTZ (1944) stated that while the therapeutic effectiveness of Salazopyrin was greatest in recent cases, patients with a long history not infrequently showed marked improvement. In two papers published in 1948 SVARTZ presented the results of a follow-up analysis of Salazopyrin treatment in acute polyarthritis as well as in chronic rheumatoid arthritis. The latter group comprised 475 cases, which in the period 1941 to 1945 had been treated with Salazopyrin (or, occasionally, salicyl-azo-thiazole or salicyl-azo-sulphapyrimidine). A questionnaire circularized in 1947 produced replies from 307 of these patients. The observation period was at least 2 years. It was found that among the 307 subjects replying to the questionnaire 104 were cured or considerably improved and 24 were moderately or slightly improved. Improvement had occurred in 66 cases, where there had been a relapse during the period of observation. Hence altogether 194 subjects had recovered or improved, i.e. 63 per cent approximately. In 1948 SVARTZ stated that periarticular Salazopyrin injections had proved to be "a valuable adjunct to oral medication of the same drug".

SINCLAIR & DUTHIE (1949) were unable to find that Salazopyrin had any specific value in the treatment of rheumatoid arthritis. It should be noted, however, that their Salazopyrin group merely comprised 20 subjects. They compared this group with 20 persons receiving gold treatment and with another group of 20 persons not undergoing any "specific" therapy. They had an observation period of 6 to 8 months. KUZELL & GARDNER (1950) used Salazopyrin in 30 cases of rheumatoid arthritis for periods from 2 months to 1 year, finding that "14 patients were symptomatically relieved in varying degree".

In recent years *phenylbutazone* (Butazolidin), often combined with aminopyrine (e.g. Butapyrin, Irgapyrin), has been tried in various rheumatic disorders. As far as the use of these drugs in rheumatoid arthritis is concerned, most authors have found that, although producing considerable subjective improvement, it is not very often that they give rise to objective improvement. For example, the E.S.R. is rarely affected, and improvement is often of short duration. CURRIE (1952), for instance, achieved objective improvement in 30 per cent of 81 cases of rheumatoid arthritis. STEPHENS *et al.* (1952) found a marked objective improvement in 41 per cent of 115 cases. STEINBROCKER *et al.* (1952) in as little as 23 per cent of 117 cases obtained an "antiarthritic effect of notable degree". CURRIE *et al.* (1953), lastly, reported objective improvement in 30 per cent of 424 cases. An additional consideration of no small importance is that most authors have reported that administration of these substances is accompanied by marked side-effects.

Hormone therapy has been widely used for rheumatoid arthritis. Chiefly female sex hormones have been given, which of course has to do with the association observed between rheumatic disease and pregnancy, parturition, menopause, etc.

Nevertheless most authors have been disappointed with the results of endocrine therapy (Cohen *et al.*, 1940; Hench *et al.*, 1942; Freyberg, 1942; Comroe, 1944; etc.). Here it may also be mentioned that trials have been made with blood transfusions from pregnant women. Most authors have obtained no results thereby, although Barsi (1947), for example, recorded protracted improvement in 64 per cent of 28 cases. However, in view of Hench *et al.*'s (1949) experiences of ACTH and Compound E, an entirely new approach has been made to the question of endocrine therapy in rheumatoid arthritis.

While some of the treatments described above have been widely used, others have not attained much popularity. Most of these forms of therapy have evidently generated heated discussions; and, owing to the aforementioned small and inadequately described groups of patients, definite conclusions regarding the effect of these treatments would not be warranted. Of course, many modes of therapy additional to those mentioned have been tried in rheumatoid arthritis, but most of them have probably achieved very limited adoption.

CAUSE OF DEATH IN RHEUMATOID ARTHRITIS

It is of course most interesting to ascertain to what extent rheumatoid arthritis causes fatal lesions. Occasionally being the cause of death, cardiac lesions have been found at autopsy and attributed to rheumatoid arthritis by some authors (Edström, 1940; Baggenstoss & Rosenberg, 1941; Baggenstoss & Rosenberg, 1943; Rosenberg *et al.*, 1943; Bayles, 1943; Baggenstoss & Rosenberg, 1944; Rosenberg *et al.*, 1944; Young & Schwedel, 1944; Clark & Bauer, 1948; Jonson *et al.*, 1949; etc.). In this connection it is worth noting that other investigations based on clinical data show that cardiac changes do not occur more often in rheumatoid arthritis patients than in normals (Rosenberg *et al.*, 1947, 1950; Sundelin, 1949; Rohlin, 1949; Sundelin & Rohlin, 1952; Rohlin & Sundelin, 1952; etc.). In some cases, moreover, autopsy has disclosed the presence of amyloidosis, renal lesions, etc., which have been ascribed to rheumatoid arthritis and occasionally have caused death (Edström, 1940; Baggenstoss & Rosenberg, 1943; Rosenberg *et al.*, 1943; Rosenberg *et al.*, 1944; etc.).

Some of the aforementioned authors have in addition specified the cause of death, in so doing having attempted to distinguish between causes which they have attributed to the rheumatic disease as such and causes for which they have made intercurrent disorders responsible. Reporting 22 cases of death among 262 patients with rheumatoid arthritis who had been under observation for 5–10 years, Edström (1940), for example, stated that 15 of these had died of the rheumatic affection. In 6 of these 15 cases the cause of death was vitium organicum cordis incompensata, in 5 it was renal incompensation (one of these exhibited extensive amyloidosis), in one case it was polyserositis, and in 3 it was

Table 6 a.

Author	Year	No. of deaths	Deaths in rheumatoid disease	Causes of death due to rheumatoid arthritis			
				Cardiac lesion %	Renal lesion %	Amyloidosis %	Gastrointestinal lesion %
Edström	1940	22	15	40 (Vitium cordis: 6 cases)	27 (Renal incompensation: 4 cases)	7 (1 case)	
Rosenberg *et al.* . . .	1944	30	10	70 (Rheumatic heart disease: 7 cases)		10 (Renal amyloidosis: 1 case)	20 (Chronic diarrhoea: 2 cases)
Ekelund	1951	77	36	19 (Heart-failure: 7 cases)		14 (Renal insufficiency: 5 cases)	

Table 6 b.

Author	Year	No. of deaths	Pneumonia, bronchopneumonia, %	Causes of death			
				Cardiac lesion %	Renal lesion %	Amyloidosis %	Gastrointestinal lesion %
Kuhns & Joplin . .	1936	76	24	20 (Endocarditis: 2 cases. Myocarditis: 13 cases)	14 (Nephritis: 11 cases)		
Benett	1943	48	17	10 (Endocarditis: 2 cases. Myocarditis: 3 cases)	8 (Nephritis: 4 cases)		8 (4 cases)
Fingerman & Andrus	1943	61	53	5 (Cardiac decompensation: 3 cases)	3 (Uraemia: 2 cases)	5 (3 cases)	
Snorrason	1950	137	18	17 (Rheumatic heart disease: 1 case. Non-rheumatic heart disease: 22 cases)	10 (Pyelonephritis: 14 cases)		

marasmus associated with bronchopneumonia etc. Rosenberg *et al.* (1943, 1944) described causes of death in 30 cases of rheumatoid arthritis. In 10 of these cases death was due to lesions that the authors associated directly with the rheumatic process, viz. rheumatic heart disease in 7 cases, renal amyloidosis in one and chronic diarrhoea in 2 cases. Studying a post-mortem series of 77 rheumatoid arthritis patients, Ekelund (1951) described it as the cause of death in 36 cases, viz. heart failure in 7 cases, renal insufficiency in 5, septic conditions in 5, agranulocytosis secondary to gold administration in 2, and profound cachexia in 17 cases (cf. Table 6a).

Other authors have recorded causes of death in rheumatoid arthritis without entering upon the question to what extent these were due to the rheumatoid affection (Kuhns & Joplin, 1936; Benett, 1943: Fingerman & Andrus, 1943; Snorrason, 1950). Pneumonia and bronchopneumonia have proved commonest among diseases leading to death. Heart diseases were the second commonest cause in the investigations published by Kuhns & Joplin (1936) and by Snorrason (1950). From the data supplied it is impossible to distinguish any other dominant disease (Table 6b).

In an occasional gold-treated patient with rheumatoid arthritis such complications have, of course, ensued as have been the direct cause of death. Many authors have reported such cases, but their incidence varies within wide limits. Although, as noted, complications following chrysotherapy will not be discussed in this treatise, it may nevertheless be mentioned that Sundelin (1948) in a series of 1904 gold-treated cases—the largest published hitherto—found a death rate of 0.36 per cent.

From the literature reviewed on the preceding pages it is evident that some authors still are doubtful of the value of chrysotherapy in rheumatoid arthritis, more especially perhaps they doubt the long-term value. In the present work an attempt will therefore be made at judging the results of gold therapy as compared with physical treatment. Both the immediate and the late results will be considered. Unfortunately it was necessary to carry out the follow-up study by means of a circularized questionary instead of by personal examination, but the study should nevertheless provide some idea of the long-term results of gold therapy for rheumatoid arthritis. It stands to reason that a number of subordinate problems also will be considered in their proper place in relation to the main questions.

CHAPTER 2

MATERIALS FOR STUDY

The work aims at studying the prognosis of rheumatoid arthritis and, chiefly, at comparing the prognoses of rheumatoid arthritis with and without gold therapy. (Cf. "Review of the Literature".) The number of cases of rheumatoid arthritis studied comprised 502 which were given gold therapy and 362 which were given other therapy. Furthermore the investigation includes studies of a group of 42 cases which were treated with hormones (cortisone and/or ACTH) combined with gold and of a group of 20 cases where hormones were combined with Salazopyrin. The discussion of these groups will be found in the appendix.

Those given gold therapy received their first course of such treatment in the period 1939–44 at the Royal Pensions Board's Hospital at Nynäshamn. These persons received in addition to gold physiotherapy of various kinds and, as required, orthopaedic treatment. During the aforementioned period or later up to the time of the follow-up examination 157 of these persons were given more than one course of gold therapy at the Pensions Board's Hospital at Nynäshamn. An occasional patient might also have been treated before, between or after the courses given at Nynäshamn at other hospitals or policlinically, but such treatment can only have gone on for a short time.

When this work was begun 579 gold-treated cases were recorded. That many patients were gold-treated for the first time in 1939–44 at the Pensions Board's Hospital, Nynäshamn. Rheumatoid arthritis was diagnosed by competent rheumatologists. Nevertheless 6 cases were sorted out because in addition to joint symptoms they presented other, often supervening, symptoms from the spine, and they therefore had to be classified as anchylosing spondylarthritis.

The follow-up was done in the period 1946–50 by means of a questionary enquiring for the patients' state of health (as compared with their state at the end of the last course of treatment) and capacity for work. Some of the patients answered only when requested to do so by the Board of Pensions.

It would have been impossible in practice to do a personal follow-up. The patients were domiciled at widely dispersed places throughout middle and northern Sweden. A follow-up which like the present one is done by means of a circularized questionary naturally may produce answers of varying reliability. In order to induce the patients to give as truthful answers as possible it was expressly stated that the data supplied were to be used for a scientific investigation and would not be associated with present pensions status, hospital charges, etc.

In 19... you were given treatment for rheumatoid arthritis at ..... For the purposes of a medical research project regarding rheumatic diseases, I should be grateful if you would answer the questions below. All you have to do is to cross out the "yes" or "no" which is the inappropriate answer to each question. Please return the completed form to me as soon as possible and not later than a month from now. A stamped and addressed return envelope is included.

Please note that any information you give will be treated with the strictest confidence and will not be seen by anyone but me. Thus your pensions status and eligibility for further treatment will in no way be prejudiced.

Are you at present feeling quite well?	Yes.	No.
Are you much better than when discharged?	Yes.	No.
Are you slightly better than when discharged?	Yes.	No.
Has the condition remained unchanged since you were discharged?	Yes.	No.
Are you worse than when you were discharged?	Yes.	No.
Have you been able to work as usual since you were discharged?	Yes.	No.
Have you been able to work only part of the time?	Yes.	No.
Have you been unable to work?	Yes.	No.
If you have been working only part of the time or not at all, has rheumatoid		
arthritis been responsible?	Yes.	No.
another illness?	Yes.	No.
difficulty in obtaining suitable employment?	Yes.	No.
unemployment?	Yes.	No.

How have you been employed since you were discharged?

Your comments:

The Pensions Board's Hospital, Nynäshamn,

Date.

FOLKE BOHMAN

Fig. 1.

Some of the returns seemed a bit obscure, of course, but in such cases supplementary evidence was often secured. Sometimes the claimed capacity for work made it easier to estimate the state of health, and vice versa. And, although some of the recorded replies might have been unreliable, it is rather unlikely that the comparison between gold therapy and other treatment would be affected thereby, because groups as large as these would have about the same proportion of inadequate replies. The questionary is reproduced in Fig. 1.

Among those gold-treated patients who were followed up, it appeared that 39 had died, and 27 could not be traced despite the Board of Pensions' and Parish Registrars' efforts to do so. Returns thus came in from 507 of the original 579 patients, but in 5 instances the data given were so unclear as to be useless. Accordingly the net number of cases analyzed was 502.

The ultimate group of gold-treated cases seems representative: the results of treatment were not a basis for selection and only 5.1 per cent of the circularized patients were unresponsive. Those who died will be discussed elsewhere.

Just as the gold-treated patients, the 362 patients studied who were managed differently underwent treatment for the first time somewhere in the period 1939–

44 at the Pensions Board's Hospitals using little or no gold therapy.[1] Whatever therapy these patients received—physical, orthopaedic or other—it was not gold, and 163 of them were treated more than once at these hospitals between 1939 and the follow-up study.

Some patients in the latter group too might have received hospital or out-patient care at other establishments between and after courses at the Pensions Board's Hospitals.

For this study 612 patients receiving therapy other than gold were recorded initially, namely all persons having first courses of general medical or physical treatment—but not gold—at the hospitals and during the period concerned. Here, too, rheumatoid arthritis was diagnosed by experienced rheumatologists. Yet 195 cases were rejected owing to doubtful diagnoses. A number of elderly patients in this group presented symptoms from some of the larger joints, and might therefore have suffered predominantly from osteoarthrosis. But most of these 195 patients had mainly subjective symptoms and more objective signs, when present, were very insignificant. The E.S.R. was normal in most cases. It would obviously be rash to rule out rheumatoid arthritis in these cases, but they were rejected in order to ensure that the investigation would have for its basis a high order of diagnostic reliability. Moreover they lacked direct counterparts among those receiving gold therapy.

Those not given chrysotherapy were followed up by the same questionary method and in the same period, 1946–50, as those given such therapy. It appeared that 7 of the patients not given gold had died, and from 39 there were no returns despite the Board of Pensions' and Parish Registrars' repeated efforts to trace them. Among the 371 returns received 9 had to be discarded because they were so vague as to be useless. For scientific study there thus remained 362 patients who underwent some form of treatment other than gold therapy.

Nor among the rheumatoid arthritis cases receiving non-gold can the rejections be considered numerous or selective enough to influence the results. The material would seem to satisfy reasonable requirements for representativeness.

With regard to the gold-treated cases, clinical criteria—history, joint status, E.S.R., mode of treatment and its immediate results for the different courses, etc.—were taken from records kept at the Pensions Board's Hospital at Nynäshamn, where all the patients concerned were treated.

According to the severity of the joint changes, the objective joint symptoms at the beginning of the first and end of the last course of treatment have been designated with one, two or three plus signs. Each joint separately has been evaluated thus, except the articulations of fingers and toes which were judged in groups, the digital joints of the right hand being one group, those of the left hand another, etc. Mild objective joint symptoms such as periarticular swelling, slightly restricted mobility, etc. were accorded one plus. The presence of hydrops

[1] Henceforth this group of patients will occasionally be termed "the controls", "the controls series", or other designations to that effect.

meant at least one additional plus. But two or three signs do not invariably indicate the presence of hydrops; instead there might have been markedly restricted mobility, anchylosis, deviations, dislocations, etc. This classification was based chiefly on the clinical picture, but when roentgen examinations were made their evidence was taken into account. The total number of plus signs for a patient would consequently represent his joint status. Where such data are considered useful, the number of plus signs per affected joint are given too. The method of recording this information is explained in the next chapter.

It would have been valuable if the marks denoting joint status could have shown whether the symptoms were suggestive of a high degree of activity (hydrops, decalcification, etc.) or indicated a low degree of activity or recovery (anchylosis, sclerosing, etc.). In practice, however, this proved impossible, because the same patient often presented a complete range of symptoms of all types.

In describing the material, the E.S.R. (the one-hour observation according to WESTERGREN) has been given for the beginning and end of each course of treatment.

Chrysotherapy was given with several different gold preparations, and various dosages were used at different times. The large majority of courses of gold treatment could be completed, but a number were discontinued because of severe complications and a few on non-medical grounds. Full specifications will be found in a subsequent chapter. In this work the immediate result of each course of gold therapy has been classified under one of the following headings: symptomless, markedly improved, slightly improved, unimproved, worse.

For those given some therapy other than gold drugs, the same clinical data as for the gold-treated cases—i.e. history, joint status, E.S.R., mode and results of treatment, etc.—have been extracted from the detailed reports on all discharged cases which are sent to the Board of Pensions by the hospitals under its supervision.

As for the gold-treated group, the joint status at the beginning of the first course and the end of the last has been represented by one, two or three plus signs, depending on the severity of the joint changes. The E.S.R. at the beginning and end of each course and the therapeutic response were also recorded similarly.

The statutory rules governing the Board of Pensions' functions in caring for the sick have imposed three restrictions on the material for study. It includes no person over 60 years of age, none who was hopelessly disabled when first seen and had a very poor prognosis, and none of the reasonably well-to-do. But, applying equally to both groups, these restrictive factors are unlikely to have significantly affected the results of this study.

The two groups studied, those treated with gold and those treated otherwise, must in addition be classified with respect to age and sex distribution. In other

Table 7. Distribution according to age at the admission to the 1st course of treatment. Gold-treated and not gold-treated patients.

Treatment	Age at the admission to the 1st course	Both sexes	
		Number	Per cent
Gold	< 20	33	6.6
	20–29	97	19.3
	30–39	134	26.7
	40–49	175	34.9
	50–ω	63	12.5
	Total	502	100
Not gold	< 20	18	5.0
	20–29	65	18.0
	30–39	125	34.5
	40–49	99	27.3
	50–ω	55	15.2
	Total	362	100

words it must be established whether they can justifiably be compared with one another.

As shown in Table 7, the patients were divided into five *age classes* showing how old they were at the beginning of the first course of treatment. The percentage of those below 20, of those between 20 and 29 and of those over 50 years old proved much the same in the group treated with gold as in that treated otherwise. In this connection it may fittingly be restated that the Board of Pensions' regulations prevented persons over 60 years old from being included.

In the 30–39 and 40–49 years age classes, which in this investigation and most others have the highest incidence of rheumatoid arthritis, the gold-treated group differed from that with other treatment. While 26.7 per cent of the former were in the 30–39 years group and 34.9 per cent in the 40–49 years age class, the proportions were almost reversed among those not given gold, viz. respectively 34.5 and 27.3 per cent, but the differences are neither probable nor significant. On the whole, thus, the patients given gold were just a bit older than those not given gold.

However, combining these two age groups, we obtain an age group of 30–49 years in which the percentage of gold-treated patients agrees remarkably well with the percentage of those not so treated, namely 61.6 per cent as against 61.8 per cent.

The age difference between the two groups studied seems inconsiderable and should have no consequences for the results. The χ^2-test applied to the age distribution of the two groups yields a P lying between 0.1 and 0.05, which does not indicate that the difference should be significant. To complete the picture we have furthermore studied the age at the time of onset of the disease. In this

Table 8. Percentual number of women in different age groups (i.e. the age at the admission to the 1st course of treatment) among gold-treated and not gold-treated patients.

Treatment	Age at the admission to the 1st course	Total number	Women	
			Number	Per cent
Gold	< 20	33	20	60.6
	20–29	97	66	68.0
	30–39	134	92	68.7
	40–49	175	120	68.6
	50–ω	63	52	82.5
	Total	502	350	69.7
Not gold	< 20	18	10	55.6
	20–29	65	40	61.5
	30–39	125	78	62.4
	40–49	99	59	59.6
	50–ω	55	27	49.1
	Total	362	214	59.1

respect, however, the two groups agreed well, and for that reason it should be unnecessary to publish the appropriate tables.

Sex Distribution (Table 8). Women were predominant in both groups. Of those receiving gold 69.7 per cent were women and of others 59.1 per cent. In an average population women should constitute about 50 per cent. In a limited sample, on the other hand, this proportion will show random deviations, which, in a small sample, might be so large that if the percentage only is considered one is tempted to believe there is a true difference, although that by no means always is the case. Since the sex distribution changes with age, the true normal figure must depend on the age of the population. However, it can be assumed to lie somewhere close to 50 per cent. And standard errors have therefore been calculated from that proportion. For the two relevant groups the standard errors are ± 2.2 and ± 2.6 per cent, and therefore that one should not expect a larger random deviation from 50 per cent than three times these standard errors. Random deviation can in other words bring the figure up to 56.6 per cent and 57.8 per cent respectively. Any higher figures obtained will deviate truly from the average population, and such differences can therefore be considered significant.

That rheumatoid arthritis has a higher incidence among women than among men has, of course, been brought out by other investigations (cf. Tables 2 and 5). However, the above figures show that in the present study there was a much larger preponderance of women among the gold-treated patients than in the group with other treatment. The difference, 10.6 ± 3.3 per cent, is statistically significant. Those treated with gold probably presented more marked symptoms,

and that might be why there was a greater preponderance of women among them. The excess of women was fairly uniformly distributed over the several age groups.

Accordingly the sex distribution was not quite the same in the two groups studied. This must consequently be taken into due account henceforth. But a further reason for grouping the patients by sex was to ascertain whether the sexes responded differently to therapy.

All the patients comprising the two groups studied did, as noted, present the clinical picture of rheumatoid arthritis. Changes uncharacteristic of this disease were not, of course, disclosed at X-ray examination, which was done in all the gold-treated cases and a lot of the others. As mentioned elsewhere cases classifiable as anchylosing spondylitis were eliminated. So were, of course, cases of osteoarthritis, Heberden's disease and other degenerative affections of the joints.

Four of the gold-treated males had a history of gonorrhoea. And as the arthritides associated with that infection are considered specific these cases will be discussed more fully. Here it may be mentioned that there was no other history of such specific infections as are said to produce arthritis.

The four men who had a history of gonorrhoea presented the picture of rheumatoid arthritis with pronounced symptoms (hydrops, etc.) in a number of joints. Thus, for example, in all of them the joints of the fingers or toes or both were involved. Exacerbating with increasing durations, changes of the type seen in rheumatoid arthritis were found at roentgen examination.

Examining the gonorrhoeal infection's association with the articular affection in these 4 cases, one finds that one of the patients developed arthritic symptoms some weeks after the infection. In due course these symptoms became worse, and gold therapy was commenced after about half a year. There was only a slight response to treatment. Later the patient was treated elsewhere as well, but at follow-up after 5.2 years there still was only slight improvement. Following gonorrhoea the remaining 3 patients had acute or subacute symptoms of polyarthritis which disappeared after some months. After that they only had negligible, chiefly subjective joint symptoms or were symptomless for respectively 4.5, 8 and 9 years, when polyarthritic symptoms set in, which were such as to warrant gold treatment. At follow-up examination after 4.8, 4.9 and 7.4 years respectively all three were considerably improved. At least in these three patients, whose rheumatoid arthritis developed many years after their gonorrhoeal infection, it seems rather unlikely that the two conditions were associated.

The chief evidence for gonorrhoea's capability of giving rise to arthritis is that gonococci have been demonstrated in effusions from arthritic joints. Yet these bacteria can be demonstrated mainly in some purulent and seropurulent and not in most forms of arthritis following gonorrhoea. Here it may be remarked that no such examination was done in the 4 cases mentioned. Moreover, in course as well as in clinical and X-ray symptoms, most arthritides after gonorrhoea on

the whole resemble rheumatoid arthritis, just as did the cases discussed here. It could perhaps be discussed whether, for such forms of polyarthritis, the gonorrhoeal infection does anything but operate as a kind of trigger-mechanism in similarity to a variety of unspecific infections.

Even if these 4 cases of polyarthritis might be considered different diagnostically, it may be emphasized that the prognosis—good for three of the cases—naturally cannot affect the series as a whole.

The material for study furthermore included 3 patients (2 gold-treated women and a man with other treatment) who, in addition to rheumatoid arthritis, had psoriasis. The association, if any, has been the subject of a lively discussion. However, most authorities maintain that, although it might exhibit certain peculiarities, the joint affection in such cases conforms with what is known as rheumatoid arthritis.

The two women who had psoriasis and received gold treatment not only responded remarkably well to therapy but were found to be considerably improved at follow-up examination 6 and 6.4 years later. The third person with psoriasis—a man given two courses of physical therapy—became a little better the first time and much better the second, but was worse at follow-up after 5.7 years. In all three the skin affection preceded joint symptoms by many years. The man's joint symptoms were more severe than the two women's.

In these patients with psoriasis and in the 4 men with a history of gonorrhoea the clinical manifestations of polyarthritis thus did not differ from those of rheumatoid arthritis. No definite association can be demonstrated. It might also be possible, of course, that disorders as prevalent as gonorrhoea or psoriasis, on the one hand, simply coincided with rheumatoid arthritis, on the other. These cases were included in the study after some doubts.

In subsequent chapters a closer study will be made of the material for study, viz. 502 cases of rheumatoid arthritis treated with gold and 362 similar cases given other treatment. The main object of this chapter is to discuss certain major sources of error. Other sources of error will be taken up in their proper context.

For the statistical analysis of the data standard procedures were used, particularly those given by Dahlberg, 1940.

CHAPTER 3

IMMEDIATE RESULTS OF THERAPY

All those who have had anything to do with gold therapy will have a strong impression that it helps, often dramatically. It is of importance to determine to what extent measurable signs and symptoms change in response to therapy. The difficulty lies in estimating within reasonable limits the severity of rheumatoid arthritis. Among its measurable manifestations the E.S.R. and the joint changes take first place; but precise evaluation of joint changes is a difficult matter, and occasional subjective estimates cannot be avoided. None of the observed patients had fever, so fever could not be used as a criterion.

Comparing first the results of the first course of gold treatment and of physical therapy without considering whether any patients underwent subsequent courses, we note in Table 9 that the gold-treated patients showed marked improvement or became symptomless far oftener than those undergoing physical therapy. (As these were a true control group they will henceforth from time to time be called the controls.) The differences are statistically significant, being 5.3 ± 1.4 per cent for the symptomless group and 37.6 ± 3.2 per cent for the markedly improved subjects. Moreover, while there were no aggravations among the gold-treated cases 1.1 per cent of the controls had become worse. There also were more unimproved and slightly improved cases among the controls. So the immediate response to gold therapy must be considered very favourable. We shall now analyze the available data in various ways. Firstly separate analyses will be made for men and women (see Table 10).

As mentioned, men formed a minority both of the gold-treated patients and of those given physical therapy, the proportion of men being 34.7 per cent in both groups combined. The difference between the groups in number of symptomless subjects was merely probable for men and not even that for women. On the other hand the large number of marked improvements following gold resulted in significant differences for both sexes, namely 42.6 ± 3.8 for women and 27.6 ± 5.4 per cent for men. As these two differences themselves differ by 15.0 ± 6.6 per cent, i.e. not quite 2.3 times the standard deviation, it seems that women tended to show considerable improvement more often than men. Statistically the latter difference is of course neither significant nor probable, but it does support the assumption that it might have been greater had the groups been more numerous. Another possibility, which we shall have occasion to look into later, is that one of the sexes might have had the disease more severely at the beginning of treatment.

Table 9. Immediate results of therapy after the 1st course in gold-treated and not gold-treated patients.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Symptomless	39	7.8±1.2	9	2.5±0.8	5.3±1.4**
Markedly improved	315	62.7±2.2	91	25.1±2.3	37.6±3.2**
Slightly improved	133	26.5±2.0	197	54.4±2.6	−27.9±3.3**
Unimproved	15	3.0±0.8	61	16.9±2.0	−13.9±2.2**
Worse	—	—	4	1.1±0.5	− 1.1±0.5
Total	502	100	362	100	—

Table 10. Immediate results of therapy after the 1st course in gold-treated and not gold-treated men and women.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Men:					
Symptomless	14	9.2±2.3	3	2.0±1.2	7.2±2.6*
Markedly improved	84	55.3±4.0	41	27.7±3.7	27.6±5.4**
Slightly improved	45	29.6±3.7	82	55.4±4.1	−25.8±5.5**
Unimproved	9	5.9±1.9	22	14.9±2.9	− 9.0±3.5*
Worse	—	—	—	—	—
Total	152	100	148	100	—
Women:					
Symptomless	25	7.1±1.4	6	2.8±1.1	4.3±1.8
Markedly improved	231	66.0±2.5	50	23.4±2.9	42.6±3.8**
Slightly improved	88	25.1±2.3	115	53.7±3.4	−28.6±4.1**
Unimproved	6	1.7±0.7	39	18.2±2.6	−16.5±2.7**
Worse	—	—	4	1.9±0.9	− 1.9±0.9
Total	350	100	214	100	—

** = statistically significant difference.

* = statistically probable difference.

The asterisks in the following tables have the same sense.

Before these results can be evaluated, the means of assessing the outcome of treatment must be specified. Changes in joint status and E.S.R. were first of all estimated and then, wherever possible, the patient's general well-being, blood picture, X-ray findings, etc. were taken into consideration. Since details of the joint status were available in hospital records and other documents, the effects of therapy could be assessed fairly accurately in this respect. Epicrises done at the end of every course of gold treatment furnished additional evidence of these patients' response.

Table 11. Immediate results of therapy after the 1st course in gold-treated and not gold-treated patients, grouped according to E.S.R. at the admission.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
E.S.R. = <20:					
Symptomless	20	13.1±2.7	5	3.1±1.4	10.0±3.0**
Markedly improved	82	53.6±4.0	57	35.2±3.8	18.4±5.5**
Slightly improved	47	30.7±3.7	75	46.3±3.9	−15.6±5.4*
Unimproved	4	2.6±1.3	25	15.4±2.8	−12.8±3.1**
Worse	—	—	—	—	—
Total	153	100	162	100	—
E.S.R. = 20–39:					
Symptomless	13	6.7±1.8	2	1.7±1.2	5.0±2.2
Markedly improved	136	69.7±3.3	23	19.3±3.6	50.4±4.9**
Slightly improved	45	23.1±3.0	70	58.8±4.5	−35.7±5.4**
Unimproved	1	0.5±0.5	22	18.5±3.6	−18.0±3.6**
Worse	—	—	2	1.7±1.2	− 1.7±1.2
Total	195	100	119	100	—
E.S.R. = 40–∞:					
Symptomless	6	3.9±1.6	2	2.5±1.7	1.4±2.3
Markedly improved	97	63.0±3.9	11	13.6±3.8	49.4±5.4**
Slightly improved	41	26.6±3.6	52	64.2±5.3	−37.6±6.4**
Unimproved	10	6.5±2.0	14	17.3±4.2	−10.8±4.7
Worse	—	—	2	2.5±1.7	− 2.5±1.7
Total	154	100	81	100	—

The term "markedly improved" indicates a marked reduction of manifest signs—for example, great decrease or clearing up of hydrops, improved mobility, materially lower E.S.R. readings. Where there had been slight joint involvement prior to treatment there would be practically none, where the joint disorders had been severe predominantly the most active ones would be much reduced.

Patients classified as "slightly improved" displayed only small alterations of the joint status and E.S.R., apart from better general health and subjective improvement. The other terms used are self-explanatory and require no special qualifications.[1]

We now come to E.S.R. changes in the two groups. Because the E.S.R. can be said to reflect the activity of the rheumatic process, the subjects were divided into 3 E.S.R. groups according to readings taken before treatment. The first group included readings under 20 mm in 1 hour, the second those from 20 to 39 mm, and the third those of 40 mm and over in 1 hour. This subdivision was

[1] This classification is largely similar to that proposed by STEINBROCKER *et al.* (1949).

chosen because it gave rise to groups comprising the same number of patients approximately. (Similar classifications recur throughout this investigation.) The results of the first course of treatment in these E.S.R. groups are given in Table 11.

The table reveals that a large number of those with a low E.S.R., i.e. less than 20 mm, before treatment had become symptomless after receiving gold. Compared with the controls the difference, 10.0 ± 3.0 per cent, was statistically significant. The difference in symptomlessness was not so marked in the higher E.S.R. groups where there instead was a preponderance in marked improvements following gold therapy. This preponderance seemed greatest in the 20–39 mm group where those given gold and improving markedly differed from the corresponding patients undergoing physical therapy by 50.4 ± 4.9 per cent. But the highest group (E.S.R.: 40 mm or more) was not far behind. There the frequency of marked improvements was 49.4 ± 5.4 per cent higher among those given gold than among the controls. These figures suggest strongly that gold treatment, as opposed to physical therapy, is more effective in patients with a high E.S.R. than in those whose E.S.R. is low or normal, whereas physical therapy is most effective in cases with a low blood sedimentation rate.

Because the E.S.R. generally is proportional to the activity of the rheumatic process, any E.S.R. alterations occurring during treatment are a valuable yardstick for the therapeutic efficacy of that treatment. E.S.R. changes recorded during the first course of treatment have therefore been collected in Table 12 (from which 37 controls had to be excluded owing to lacking figures for the E.S.R. at the end of treatment). The patients were classified into the same groups as before according to their initial E.S.R.: and the E.S.R. readings were divided into three groups, viz. reductions over 25 mm in 1 hour, reductions from 25 to 6 mm in 1 hours, and a group where the E.S.R. reading was reduced 5 to 1 mm in 1 hour, remained unchanged or increased.

Most of the patients in the group of initial E.S.R. readings below 20 mm showed few if any changes whatever treatment they had received. Falling within the range of normal variation, changes of at most 5 mm have been listed separately.

Most cases where the initial E.S.R. was moderately high (20–39 mm) presented a considerable reduction following gold treatment. After physical therapy this was not so common.

Following gold therapy more than half of the initially high E.S.R. values (over 40 mm) showed a reduction of more than 25 mm, but after physical therapy the same thing was significantly less frequent.

Accordingly gold therapy causes a greater reduction of the E.S.R. than other treatment does, a difference which becomes more accentuated the higher the initial E.S.R. reading.

An interesting point is obviously how the immediate results of therapy are related to the joint disability. In this examination the degree of articular dis-

Table 12. Changes in E.S.R. during the 1st course from the admission to the discharge in gold-treated and not gold-treated patients, grouped according to E.S.R. at the admission.

Change of E.S.R. (in mm)	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
E.S.R. at admission = <20:					
Decrease of 6 mm or more	49	32.0±3.8	27	18.7±3.2	13.3±5.0*
Decrease of 1–5 mm, or no change or increase	104	68.0±3,8	117	81.3±3.2	−13.3±5.0*
Total	153	100	144	100	—
E.S.R. at admission = 20–39:					
Decrease of more than 25 mm . .	13	6.7±1.8	1	0.9±0.9	5.8±2.0*
Decrease of 6–25 mm	141	72.3±3.2	57	52.8±4.8	19.5±5.8**
Decrease of 1–5 mm, or no change or increase	41	21.0±2.9	50	46.3±4.8	−25.3±5.6**
Total	195	100	108	100	—
E.S.R. at admission = 40–ω:					
Decrease of more than 25 mm . .	80	51.9±4.0	22	30.1±5.4	21.8±6.7**
Decrease of 6–25 mm	53	34.4±3.8	30	41.1±5.8	− 6.7±6.9
Decrease of 1–5 mm, or no change or increase	21	13.6±2.8	21	28.8±5.3	−15.2±6.0*
Total	154	100	73	100	—

orders was denoted by one, two or three plus signs, as explained in the chapter on materials for study. Mild signs (periarticular swelling, slightly restricted mobility, etc.) were designated as one plus sign, the presence of hydrops was expressed by at least two plus. But two or three plus signs did not always signify the presence of hydrops, they might also denote grave disturbances such as anchylosis, dislocation, etc. The total number of plus signs gave a rough measure of a patient's joint status. Of course such a measure of the joint status is not perfectly objective—but no method exists whereby a particular patient's joint condition can be exactly codified in a single expression. As noted, this method does not reflect the activity of the rheumatic process, but as that function is roughly fulfilled by the E.S.R. this is of secondary importance here. To be on the safe side a correlation was performed regarding the association, if any, between the gross joint manifestations per person and the average condition of each joint. The results are given in Table 13.

The table shows that there was a moderately strong correlation between the total number of plus signs per person and the mean number per affected joint, but it was not strong enough to make unnecessary a study of the results when broken down in accordance with the mean number of plus per affected joint.

Table 13. Correlation between the number of plus per individual and the mean number of plus per affected joint and individual at the admission to the 1st course of treatment. Gold-treated and not gold-treated men and women.

Treatment and sex	Number of cases	$r \pm \varepsilon_r$
Gold-treated men	152	$+0.32 \pm 0.07$
» women	350	$+0.39 \pm 0.05$
Not gold-treated men	148	$+0.15 \pm 0.08$
» » women	214	$+0.39 \pm 0.06$

Table 14. Immediate results of therapy after the 1st course in gold-treated and not gold-treated patients, grouped according to the state of the joints at the admission.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
State of the joints = <8 plus:					
Symptomless	28	14.7 ± 2.6	4	4.3 ± 2.1	10.4 ± 3.3**
Markedly improved	104	54.5 ± 3.6	23	25.0 ± 4.5	29.5 ± 5.8**
Slightly improved	56	29.3 ± 3.3	51	55.4 ± 5.2	-26.1 ± 6.2**
Unimproved	3	1.6 ± 0.9	11	12.0 ± 3.4	-10.4 ± 3.5*
Worse	—	—	3	3.3 ± 1.9	-3.3 ± 1.9
Total	191	100	92	100	—
State of the joints = 8–12 plus:					
Symptomless	10	5.3 ± 1.6	2	1.6 ± 1.1	3.7 ± 1.9
Markedly improved	135	72.2 ± 3.3	36	29.3 ± 4.1	42.9 ± 5.3**
Slightly improved	36	19.3 ± 2.9	67	54.5 ± 4.5	-35.2 ± 5.4**
Unimproved	6	3.2 ± 1.3	18	14.6 ± 3.2	-11.4 ± 3.5**
Worse	—	—	—	—	—
Total	187	100	123	100	—
State of the joints = 13 plus or more:					
Symptomless	1	0.8 ± 0.8	3	2.0 ± 1.2	-1.2 ± 1.4
Markedly improved	76	61.3 ± 4.4	32	21.8 ± 3.4	39.5 ± 5.6**
Slightly improved	41	33.1 ± 4.2	79	53.7 ± 4.1	-20.6 ± 5.9**
Unimproved	6	4.8 ± 1.9	32	21.8 ± 3.4	-17.0 ± 3.9**
Worse	—	—	1	0.7 ± 0.7	-0.7 ± 0.7
Total	124	100	147	100	—

However, before that is done it is convenient to relate the results of therapy to the total number of plus signs per person. Accordingly the patients were classified in three groups: those with less than 8 plus, those with 8 plus to 12 plus and those with 13 plus or over (Table 14).

It appears that gold therapy made patients with slight joint signs symptom-

less more often than patients with severe joint involvement. In the aforementioned groups respectively 14.7, 5.3, and 0.8 per cent of the patients became symptomless. This was expected, for joint abnormalities of the severer type are not often wholly reversible. However, after grouping together those who became symptomless and those who improved markedly, we find about the same percentages in the mild and moderate groups of joint abnormalities and a somewhat lower proportion in the last group, the respective figures being 69.2, 77.5, and 62.1 per cent. Physical therapy had a similar relationship to the degree of joint involvement. 29.3 per cent of those with mild joint symptoms became symptomless or were markedly improved following physical therapy, while the corresponding figures for those with moderate and severe symptoms respectively were 30.9 and 23.8 per cent.

The frequency of marked improvement following gold was significantly higher than after physical therapy for all three classes of joint involvement. On the other hand "slight improvement" and "unchanged" consistently showed a significantly higher frequency after physical therapy than after gold, except for unimproved cases with slight symptoms where the difference was probable. Only the greater proportion of those with mild symptoms became symptomless after gold, the figures being 14.7 per cent for the gold-treated cases and 4.3 per cent for the controls, implying that the difference is statistically significant. Obviously the reason for this must be looked for in the irreversibility of severe, and to some extent of moderate, joint symptoms.

After this analysis we are ready to study the results broken down in accordance with joint abnormalities of various degrees, i.e. the average number of plus signs per affected joint. As will be realized, neither the former nor the latter classification is wholly satisfactory, but in conjunction they should nevertheless furnish a fairly true picture of the situation. M (plus) per joint for gold-treated subjects had its median at 1.34 plus, with the lower quartile at 1.12 plus and the upper quartile at 1.62 plus. Hence the subjects were divided into those with 1.0 plus–1.1 plus, those with 1.2 plus–1.4 plus and those with 1.5 plus or more per affected joint (Table 15).

Here, too, gold treatment was markedly superior to physical therapy whatever the degree of the joint disorders. Thus, while the frequency of marked improvement was significantly higher after gold than after physical therapy, unimproved and aggravated cases were seen more often among those undergoing physical therapy. As before, a higher percentage of the controls than of the gold-treated cases showed slight improvement. (These differences are statistically significant.)

These results indicate that gold treatment is far superior to physical therapy, both when the joint symptoms are mild and when they are more severe.

In evaluating the immediate results of therapy the history's length must be taken into due account. Clearly the duration and severity of rheumatoid arthritis are not proportional to one another, even if those with a long history

Table 15. Immediate results of therapy after the 1st course in gold-treated and not gold-treated patients, grouped according to the number of plus per affected joint at the admission.

Number of plus per affected joint	Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
		Number	Per cent	Number	Per cent	
1.0–1.1	Symptomless	16	12.1±2.8	8	5.6±1.9	6.5±3.4
	Markedly improved	82	62.1±4.2	38	26.4±3.7	35.7±5.6**
	Slightly improved	32	24.2±3.7	70	48.6±4.2	−24.4±5.6**
	Unimproved or worse	2	1.5±1.1	28	19.4±3.3	−17.9±3.5**
	Total	132	100	144	100	—
1.2–1.4	Symptomless	12	7.3±2.0	—	—	7.3±2.0**
	Markedly improved	101	61.2±3.8	31	25.2±3.9	36.0±5.4**
	Slightly improved	47	28.5±3.5	71	57.7±4.5	−29.2±5.7**
	Unimproved or worse	5	3.0±1.3	21	17.1±3.4	−14.1±3.6**
	Total	165	100	123	100	—
1.5–ω	Symptomless	11	5.4±1.6	1	1.1±1.1	4.3±1.9
	Markedly improved	132	64.4±3.3	22	23.2±4.3	41.2±5.4**
	Slightly improved	54	26.3±3.1	56	58.9±5.0	−32.6±5.9**
	Unimproved or worse	8	3.9±1.4	16	16.8±3.8	−12.9±4.0**
	Total	205	100	95	100	—

often have more destructive (dislocations, anchyloses, etc.) and hence more intractable joint signs. (The procedure for recording the joint status used here does not always bring out this distinction.) Not seldom, however, patients with a very short history present very severe joint disorders. It appears, therefore, that the significant factor is the intensity of the rheumatic process. Another question is whether the joint disorder, whatever its severity, might not in time become more intractable. The association between the immediate results of the first course of treatment and the duration of illness appears from Table 16. The periods concerned have been divided into three classes, viz. histories of less than one year, those of 1–2.9 years and those of 3 years or longer.

The effectiveness of gold was about the same in rheumatoid arthritis of long duration as in that of short duration. Arranged in order of lengthening history, 71.9, 73.0, and 67.9 per cent of the gold-treated cases either became symptomless or showed marked improvement. The corresponding percentages for controls declined with lengthening histories. Those who had been ill less than a year became symptomless or markedly improved in 34.3 per cent of the cases and those who had been ill more than 3 years in 21.9 per cent of the cases. Only just exceeding twice its standard error, the difference between these two frequencies is not statistically significant.

Evidently gold is superior to physical therapy in the treatment of rheumatoid

Table 16. Immediate results of therapy after the 1st course in gold-treated and not gold-treated patients, grouped according to the duration of the disease.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Duration = < 1 year:					
Symptomless	13	10.2±2.7	4	2.8±1.4	7.4±3.0
Markedly improved	79	61.7±4.3	45	31.5±3.9	30.2±5.8**
Slightly improved	29	22.7±3.7	75	52.4±4.2	−29.7±5.6**
Unimproved	7	5.5±2.0	16	11.2±2.6	− 5.7±3.3
Worse	—	—	3	2.1±1.2	− 2.1±1.2
Total	128	100	143	100	—
Duration = 1.0–2.9 years:					
Symptomless	9	5.7±1.8	1	1.0±1.0	4.7±2.1
Markedly improved	107	67.3±3.7	25	23.8±4.2	43.5±5.6**
Slightly improved	41	25.8±3.5	59	56.2±4.8	−30.4±5.9**
Unimproved	2	1.3±0.9	20	19.0±3.8	−17.7±3.9**
Worse	—	—	—	—	—
Total	159	100	105	100	—
Duration = 3 years or more:					
Symptomless	17	7.9±1.8	4	3.5±1.7	4.4±2.5
Markedly improved	129	60.0±3.3	21	18.4±3.6	41.6±4.9**
Slightly improved	63	29.3±3.1	63	55.3±4.7	−26.0±5.6**
Unimproved	6	2.8±1.1	25	21.9±3.9	−19.1±4.1**
Worse	—	—	1	0.9±0.9	− 0.9±0.9
Total	215	100	114	100	—

arthritis of both long and short duration, at least judging by the immediate results. Whether the history was short, moderate or long the percentage of marked improvements was significantly higher after gold than after physical treatment. The same was true when those who became symptomless were grouped together with the cases showing marked improvement. A significantly higher percentage of the controls with moderately long and long histories were unchanged than of the gold-treated subjects.

Accordingly gold appears to be more effective than physical therapy in the treatment of rheumatoid arthritis of both long and short duration. The former mode of treatment, moreover, seems more or less independent of the history's length, whereas physical therapy tends to grow progressively less effective the longer the history.

Generally speaking, therefore, the immediate results of gold treatment are on the whole better than those of physical therapy, which in the present investigation was reflected in improvement of the joint condition and diminution of the E.S.R. value.

Table 17. Comparison between gold-treated and not gold-treated patients with regard to the state of the joints and to E.S.R. on admission to the 1st course of treatment and with regard to the duration of the disease.

At the admission to the 1st course		Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
		Number	Per cent	Number	Per cent	
State of the joints	< 8 plus	191	38.0 ± 2.2	92	25.4 ± 2.3	12.6 ± 3.2**
	8–12 »	187	37.3 ± 2.2	123	34.0 ± 2.5	3.3 ± 3.3
	13–ω »	124	24.7 ± 1.9	147	40.6 ± 2.6	−15.9 ± 3.2**
E.S.R.	< 20 mm	153	30.5 ± 2.1	162	44.8 ± 2.6	−14.3 ± 3.3**
	20–39 »	195	38.8 ± 2.2	119	32.9 ± 2.5	5.9 ± 3.3
	40–ω »	154	30.7 ± 2.1	81	22.4 ± 2.2	8.3 ± 3.0*
Duration	< 1.0 year	128	25.5 ± 1.9	143	39.5 ± 2.6	−14.0 ± 3.2**
	1.0–2.9 years	159	31.7 ± 2.1	105	29.0 ± 2.4	2.7 ± 3.2
	3.0–ω »	215	42.8 ± 2.2	114	31.5 ± 2.4	11.3 ± 3.3**

Having contrasted gold and physical therapy with respect to E.S.R., joint status and duration, we now have to consider whether the two groups of patients were comparable in the sense that they had the disease with equal severity. This is done in Table 17.

Taking the patients as a whole without distinguishing between men and women, we note that subjects with less than 8 plus were overrepresented among those receiving gold. Though fairly equally distributed, those with 8 plus–12 plus included a small preponderance of gold-treated patients. Those with 13 plus or more were significantly overrepresented among the controls. The position is rather different, however, when the average number of plus signs per affected joint in the gold-treated group is compared with that in the controls; then, as will be seen, the gold-treated cases proved slightly more severe. In the group of mild joint alterations, i.e. those with 1.0 plus–1.1 plus per affected joint, the controls were 13.5 ± 3.3 per cent more numerous than the gold-treated subjects, a difference which is significant. In the group with moderate joint affections (1.2 plus–1.4 plus) the proportions of gold-treated and control cases were about the same. In the group with severe joint disability (1.5 plus and over), on the other hand, the frequency of gold-treated cases was significantly higher than that of the controls, the difference being 14.6 ± 3.2 per cent.

The table shows, moreover, that the "40 mm or over" E.S.R. group included a majority of gold-treated patients and that with readings under 20 mm a majority of those receiving physical therapy. This suggests that gold therapy was used in the more active cases.

It will be seen that the majority of those with moderately long and long histories (1–2.9 years and 3 years or over) had received gold treatment, and that most of those with histories shorter than 1 year had undergone physical therapy. The longer histories for the gold-treated patients probably indicate that gold

Table 18. Comparison between men and women with regard to the state of the joints and E.S.R. on admission to the 1st course of treatment and with regard to the duration of the disease.

Treatment	At the admission to the 1st course		Men		Women		Differences men – women
			Number	Per cent	Number	Per cent	
Gold	State of the joints	< 8 plus	71	46.7 ± 4.0	120	34.3 ± 2.5	12.4 ± 4.7*
		8–12 »	62	40.8 ± 4.0	125	35.7 ± 2.6	5.1 ± 4.8
		13 plus–ω	19	12.5 ± 2.7	105	30.0 ± 2.4	−17.5 ± 3.6**
		Total	152	100	350	100	—
	E.S.R.	< 20 mm	62	40.8 ± 4.0	91	26.0 ± 2.3	14.8 ± 4.6**
		20–39 »	55	36.2 ± 3.9	140	40.0 ± 2.6	− 3.8 ± 4.7
		40–ω »	35	23.0 ± 3.4	119	34.0 ± 2.5	−11.0 ± 4.2*
		Total	152	100	350	100	—
	Duration	< 1 year	48	31.6 ± 3.8	80	22.9 ± 2.2	8.7 ± 4.4
		1.0–2.9 years	52	34.2 ± 3.8	107	30.6 ± 2.5	3.6 ± 4.5
		3.0 years or more	52	34.2 ± 3.8	163	46.6 ± 2.7	−12.4 ± 4.7*
		Total	152	100	350	100	—
Not gold	State of the joints	< 8 plus	32	21.6 ± 3.4	60	28.0 ± 3.1	− 6.4 ± 4.6
		8–12 »	57	38.5 ± 4.0	66	30.8 ± 3.2	7.7 ± 5.1
		13 plus–ω	59	39.9 ± 4.0	88	41.1 ± 3.4	− 1.2 ± 5.2
		Total	148	100	214	100	—
	E.S.R.	< 20 mm	84	56.8 ± 4.1	78	36.4 ± 3.3	20.4 ± 5.3**
		20–39 »	36	24.3 ± 3.5	83	38.8 ± 3.3	−14.5 ± 4.8**
		40–ω »	28	18.9 ± 3.2	53	24.8 ± 3.0	− 5.9 ± 4.4
		Total	148	100	214	100	—
	Duration	< 1 year	64	43.2 ± 4.1	79	36.9 ± 3.3	6.3 ± 5.3
		1.0–2.9 years	38	25.7 ± 3.6	67	31.3 ± 3.2	− 5.6 ± 4.8
		3.0 years or more	46	31.1 ± 3.8	68	31.8 ± 3.2	− 0.7 ± 5.0
		Total	148	100	214	100	—

was not tried until other modes of treatment had proved unsuccessful. Consequently it is reasonable to suppose that the gold-treated patients were afflicted with rheumatoid arthritis more severely than the controls.

At this point it is appropriate to examine whether there was any relationship between sex and severity of the rheumatic process. In Table 18 the several classes of joint status, E.S.R. and history have been subdivided according to the patients' sex. It will be seen that gold-treated women were on the whole more severely ill. In addition mild joint signs and low E.S.R. values were commoner in men. (Statistically speaking these differences were either probable or signifi-

Table 19. Immediate results after the 1st course of treatment in gold-treated and not gold-treated patients. Weighted means with regard to the duration of the disease, E.S.R. and the state of the joints at the beginning of the 1st course.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Symptomless or markedly improved	279	71.0±2.3	72	25.4±2.6	45.6±3.5**
Slightly improved	100	25.4±2.2	159	56.0±2.9	−30.6±3.6**
Unimproved or worse . .	14	3.6±0.9	53	18.7±2.3	−15.1±2.5**
Total	393	100	284	100	—

cant.) Women also had long histories (of more than 3 years) oftener than men, the difference being probable.

While the joint status and history statistically were much the same for men and women undergoing physical therapy, the general tendency was the same as that in the gold-treated cases, i.e. greater severity in women. Women had high E.S.R. values significantly oftener than men.

Women thus seem to have had the disease a bit more severely than men in both therapeutic groups. But the difference in the proportion of women in the two groups although significant was small and did not seem of any very great importance.

Ideally two series which are subjected to statistical analysis should be identical except for the factor studied. Whenever possible such a state of affairs is ensured by treating a consecutive series of patients by two methods alternately. Under the conditions of the present investigation this was obviously out of the question. As identical series could not be obtained, then, the two groups had to be weighted in order to yield compatible results. In other words the various subgroups were proportionalized so as to become equally represented in the two main groups. The results of this procedure are given in Table 19.

Table 19 reveals that the difference between the gold-treated patients and those receiving physical therapy was much more marked than one would expect from the original table over the two groups. The frequency of symptomlessness or marked improvement following gold treatment was thus 71.0 ± 2.3 per cent and after physical therapy 25.4 ± 2.6 per cent. Hence the gold-treated cases became symptomless or improved considerably 45.6 ± 3.5 per cent oftener than the controls. On the other hand, while gold treatment produced slight improvement in 25.4 ± 2.2 per cent of the cases, physical therapy did so in 56.0 ± 2.9 per cent. The difference between these two percentages is significant. Lastly, the frequency of unimproved or aggravated cases was 3.6 ± 0.9 per cent following gold and 18.7 ± 2.3 per cent after physical therapy. As far as the immediate results are concerned, the figures given in this paragraph provide clear and unquestionable evidence of the superiority of gold treatment over physical therapy of rheumatoid arthritis.

CHAPTER 4

PATIENTS GIVEN MORE THAN ONE COURSE OF TREATMENT

The results of the first course have hitherto been discussed regardless of whether any patients were subsequently given additional courses. This chapter will be devoted to cases treated two or more times. Persons were treated more than once because, either

1. they showed inadequate improvement after a course, or
2. they had relapsed after the preceding course.

To begin with a survey of the incidence of repeated treatments will be provided for those treated with gold as well as for those treated otherwise (Table 20).

The table reveals that repeated courses seemed more frequent among those not given gold. One finds that 68.7 per cent of the gold-treated patients were given one course only, the corresponding figure for those not given gold being 55 per cent. The difference is 13.7 ± 3.3 per cent and statistically significant. This is in itself an interesting piece of information, chiefly because those receiving gold on the whole had the disease more severely, which was shown in the preceding chapter. On the average those given more than two courses of treatment also included a higher proportion of patients not given gold than of gold-treated patients.

Next repeated treatment has to be studied more closely. In other words one must find the percentage of inadequate improvements and of relapses after the preceding course. Such calculations were based on available case notes.

When those given two courses only were admitted to the 2nd course, 57.7 per cent of those given gold and 63.3 per cent of those not given gold were worse (Table 21).

Among those who were given more than 2 courses 58.5 per cent of the gold-treated patients were worse and so were 58.9 per cent of those who had received no gold at the beginning of the 2nd course. On admission to the 3rd course 73.6 per cent of the gold-treated patients and 53.4 per cent of those not treated with gold showed impairment. Owing to the small number of cases the difference could be random. At all events no obtainable differences are statistically probable or significant. The changes mainly considered were the alterations of the joint status from the end of one course till the beginning of the next.

If reference is made to the E.S.R. instead (Table 22), however, one finds that

Table 20. Percentual distribution according to the number of courses of treatment.

Number of courses	Gold-treated		Not gold-treated	
	Number	Per cent	Number	Per cent
1	345	68.7	199	55.0
2	104	20.7	90	24.9
3	38	7.6	58	16.0
4	10	2.0	11	3.0
5	5	1.0	3	0.8
6	—	—	1	0.3
Total	502	100	362	100

Table 21. Gold-treated and not gold-treated patients given more than one course of treatment, distributed according to the reason for the repeated treatment.

Treatment	Patients given more than one course	The reason for the repeated treatment		Total	Cases given a 2nd and a 3rd course because of impairment in per cent of all readmitted
		Inadequate or no improvement	Impairment		
Gold	Cases given 2 courses	44	60	104	57.7 ± 4.8
	Cases given more than 2 courses	22	31	53	58.5 ± 6.8
	Cases admitted to the 2nd course	66	91	157	58.0 ± 3.9 [1]
	Cases admitted to the 3rd course	14	39	53	73.6 ± 6.1 [1]
Not gold	Cases given 2 courses	33	57	90	63.3 ± 5.1
	Cases given more than 2 courses	30	43	73	58.9 ± 5.8
	Cases admitted to the 2nd course	63	100	163	61.3 ± 3.8 [2]
	Cases admitted to the 3rd course	34	39	73	53.4 ± 5.8 [2]

[1] Difference = −15.6 ± 7.2. [2] Difference = 7.9 ± 6.9.

it had increased from the end of the first course till the beginning of the second course in 56.7 per cent of gold-treated cases and in only 34.4 per cent of those given no gold. The difference is statistically significant. In other words, if one goes by the E.S.R., it appears as though impairment at the beginning of a subsequent course occurred less frequently among those not given gold than among gold-treated patients. However, even if it does so with marked aggravations, it must not be supposed that the E.S.R. parallels the impairment exactly. Therefore it is impossible to draw precise conclusions regarding the reasons for the repetition of the course in these cases.

The question now arises whether the disease in those cases which were treated more than once somehow differed in character from those requiring one course only. The joint status, E.S.R. and duration are in Table 23 compared for those treated once and those treated more than once.

The milder cases, those with a joint status denoted by less than 8 plus signs,

Table 22. Gold-treated and not gold-treated patients percentually distributed according to changes of E.S.R. between two courses of treatment.

Changes of E.S.R. between the discharge from one course and the admission to the next course of treatment	Gold-treated				Not gold-treated			
	Changes between				Changes between			
	1st–2nd course		2nd–3rd course		1st–2nd course		2nd–3rd course	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Decrease of 26 mm or more	4	2.5	1	1.9	12	7.4	3	4.1
Decrease of 6–25 mm . . .	22	14.0	8	15.1	32	19.6	16	21.9
No change (variation 5 mm)	42	26.8	12	22.6	63	38.7	25	34.2
Increase of 6–25 mm . . .	55	35.0	20	37.7	41	25.2	20	27.4
Increase of 26 mm or more	34	21.7	12	22.6	15	9.2	9	12.3
Total	157	100	53	100	163	100	73	100
Total number of cases with increase	89	56.7 ± 4.0 [1]	32	60.4 ± 6.7 [2]	56	34.4 ± 3.7 [1]	29	39.7 ± 5.7 [2]

[1] Difference gold-treated – not gold-treated $= 22.3 \pm 5.4$**

[2] » » – » » $= 20.7 \pm 8.8$.

are underrepresented among patients given more than one course of gold treatment. Conversely those with more severe joint disturbances are overrepresented, but the difference attains statistical significance only when all those with more than 7-plus joints are grouped together.

Here it was considered unnecessary to classify the patients according to the mean number of plus signs per affected joint: this would not be a comparison between groups treated with gold and groups treated otherwise but between separate cases in each of these groups.

It would seem that also those gold-treated patients with a low E.S.R. (under 20 mm) are underrepresented. The difference is probable, as is the difference between those with a high E.S.R. (40 mm or more) who very likely are overrepresented.

A corresponding deviation can additionally be found with respect to the duration of the disease. Gold-treated patients with disease durations in excess of one year seem overrepresented among those who were treated more than once, although the difference is not statistically significant.

To sum up, it can be asserted that those patients who were treated with gold more than once on the whole seem to have had rheumatoid arthritis more severely at the beginning of the first course of treatment.

With regard, finally, to those patients who were not treated with gold, similar deviations seem to have been presented in a lesser degree. The difference is statistically significant only for the duration of the disease, but not for the E.S.R. and joint status.

The results of treatment after a varying number of courses are given in Table

Table 23. Comparison between cases given one course of treatment and cases given several courses with regard to the state of the joints and E.S.R. on admission to the 1st course and with regard to the duration of the disease.

Treatment	At the admission to the 1st course		Cases given one course		Cases given more than one course		Differences one course – more than one course
			Number	Per cent	Number	Per cent	
Gold	State of the joints	< 8 plus	150	43.5 ± 2.7	41	26.1 ± 3.5	17.4 ± 4.4**
		8–12 »	121	35.1 ± 2.6	66	42.0 ± 3.9	– 6.9 ± 4.7
		13 plus–ω	74	21.4 ± 2.2	50	31.8 ± 3.7	– 10.4 ± 4.3
		Total	345	100	157	100	—
	E.S.R	< 20 mm	118	34.2 ± 2.6	35	22.3 ± 3.3	11.9 ± 4.2*
		20–39 »	135	39.1 ± 2.6	60	38.2 ± 3.9	0.9 ± 4.7
		40–ω »	92	26.7 ± 2.4	62	39.5 ± 3.9	– 12.8 ± 4.6*
		Total	345	100	157	100	—
	Duration	< 1 year	93	27.0 ± 2.4	35	22.3 ± 3.3	4.7 ± 4.1
		1.0–2.9 years	102	29.6 ± 2.5	57	36.3 ± 3.8	– 6.7 ± 4.5
		3.0 years or more	150	43.5 ± 2.7	65	41.4 ± 3.9	2.1 ± 4.7
		Total	345	100	157	100	—
Not gold	State of the joints	< 8 plus	50	25.1 ± 3.1	42	25.8 ± 3.4	– 0.7 ± 4.6
		8–12 »	76	38.2 ± 3.4	47	28.8 ± 3.5	9.4 ± 4.9
		13 plus–ω	73	36.7 ± 3.4	74	45.4 ± 3.9	– 8.7 ± 5.2
		Total	199	100	163	100	—
	E.S.R.	< 20 mm	99	49.7 ± 3.5	63	38.7 ± 3.8	11.0 ± 5.2
		20–39 »	58	29.1 ± 3.2	61	37.4 ± 3.8	– 8.3 ± 5.0
		40–ω »	42	21.1 ± 2.9	39	23.9 ± 3.3	– 2.8 ± 4.4
		Total	199	100	163	100	—
	Duration	< 1 year	88	44.2 ± 3.5	55	33.7 ± 3.7	10.5 ± 5.1
		1.0–2.9 years	44	22.1 ± 2.9	61	37.4 ± 3.8	– 15.3 ± 4.8**
		3.0 years or more	67	33.7 ± 3.4	47	28.8 ± 3.5	4.9 ± 4.9
		Total	199	100	163	100	—

24, in which are compared the patients' status at the end of the last and the beginning of the first course.

Both among gold-treated patients and those not receiving gold the number of symptomless and markedly improved cases apparently tends to be smaller and the number of unimproved or aggravated cases higher after each course of treatment. And this indicates that the more intractable cases are those which are treated more than once. Yet the only groups displaying a statistically significant difference are those becoming symptomless after the first and second course of

Table 24. Immediate results after the last course of treatment in gold- treated and not gold-treated patients given different number of courses.

Immediate results	Number of courses of treatment					
	1 course		2 courses		3 or more courses	
	Number	Per cent	Number	Per cent	Number	Per cent
Gold-treated patients:						
Symptomless	35	10.1±1.6 [1]	1	1.0±1.0 [1]	—	—
Markedly improved	210	60.9±2.6	67	64.4±4.7	25	47.2±6.9
Slightly improved	90	26.1±2.4	25	24.0±4.2	14	26.4±6.1
Unimproved or worse	10	2.9±0.9	11	10.6±3.0	14	26.4±6.1
Total	345	100	104	100	53	100
Not gold-treated patients:						
Symptomless	8	4.0±1.4	2	2.2±1.5	—	—
Markedly improved	69	34.7±3.4	24	26.7±4.7	14	19.2±4.6
Slightly improved	80	40.2±3.5	33	36.7±5.1	28	38.4±5.7
Unimproved or worse	42	21.1±2.9	31	34.4±5.0	31	42.5±5.8
Total	199	100	90	100	73	100

[1] The difference 1 course – 2 courses = 9.1±1.9**

Table 25. Immediate results after the last course of treatment in gold-treated and not gold-treated patients given one or more than one course.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Cases given one course					
Symptomless	35	10.1±1.6	8	4.0±1.4	6.1±2.1*
Markedly improved	210	60.9±2.6	69	34.7±3.4	26.2±4.3**
Slightly improved	90	26.1±2.4	80	40.2±3.5	–14.1±4.2**
Unimproved	10	2.9±0.9	42	21.1±2.9	–18.2±3.0**
Worse	—	—	—	—	—
Total	345	100	199	100	—
Cases given more than one course					
Symptomless	1	0.6±0.6	2	1.2±0.9	– 0.6±1.1
Markedly improved	92	58.6±3.9	38	23.3±3.3	35.3±5.1**
Slightly improved	39	24.8±3.4	61	37.4±3.8	–12.6±5.1
Unimproved	17	10.8±2.5	35	21.5±3.2	–10.7±4.1*
Worse	8	5.1±1.8	27	16.6±2.9	–11.5±3.4**
Total	157	100	163	100	—

Table 26. Patients re-admitted for a 2nd and a 3rd course of treatment because of inadequate improvement, compared with patients re-admitted because of impairment after the discharge. Both groups percentually distributed according to the immediate results after the last course of treatment.

Treatment	Immediate results after the last course	Re-admissions for a 2nd and a 3rd course because of: Inadequate improvement — Number	Inadequate improvement — Per cent	Impairment after the discharge — Number	Impairment after the discharge — Per cent	Differences
Gold	Symptomless or markedly improved	56	70.0±5.1	62	47.7±4.4	22.3±6.7**
	Slightly improved	18	22.5±4.7	35	26.9±3.9	− 4.4±6.1
	Unimproved	5	6.3±2.7	21	16.2±3.2	− 9.9±4.2
	Worse	1	1.3±1.3	12	9.2±2.5	− 7.9±2.8*
	Total	80	100	130	100	—
Not gold	Symptomless or markedly improved	36	37.1±4.9	18	12.9±2.8	24.2±5.6**
	Slightly improved	43	44.3±5.0	46	33.1±4.0	11.2±6.4
	Unimproved	15	15.5±3.7	39	28.1±3.8	−12.6±5.3
	Worse	3	3.1±1.8	36	25.9±3.7	−22.8±4.1**
	Total	97	100	139	100	—

gold treatment. But this perhaps is not too helpful—the line between absence of symptoms and marked improvement is sometimes rather diffuse.

Comparing the results of gold treatment and of other therapy after one and after more than one course (Table 25), one finds a far better response to gold therapy in both groups.

Thus the proportion of markedly improved patients was higher among those given gold, after both one and many courses. Unimproved or aggravated cases, on the other hand, were relatively more numerous among patients not given gold. The differences are statistically significant or probable. Only the first course of gold treatment produced a greater percentage of symptomless cases than other treatment. The difference is statistically probable: as mentioned, the number of symptomless patients given gold decreases as the number of courses increases. In this connection it is interesting to note that for patients receiving more than one course of gold treatment the median of the time interval between the beginning of the first and the end of the last course is 1.92 years, and for those not given gold 2.0 years. The corresponding upper quartiles are 3.17 and 3.13 years.

The response to repeated treatment in cases which showed inadequate improvement or relapsed after the preceding course of treatment will be found in Table 26. It compares the patients' condition at the end of the last course with their condition at the beginning of the first course.

Table 27. Immediate results after the last course of treatment in gold-treated and not gold-treated patients given repeated courses. Changes in E.S.R. between the discharge from the 1st or the 2nd course of treatment and the admission to the following course, and differences between the cases with decreased or unchanged E.S.R. and the cases with increased E.S.R.

Immediate results after the last course	Changes in E.S.R. between the courses: Decrease, no change, or increase 5 mm at most		Increase 6 mm or more		Differences
	Number	Per cent	Number	Per cent	
Gold-treated:					
Symptomless or markedly improved	57	64.0±5.1	61	50.4±4.5	13.6±6.8
Slightly improved	26	29.2±4.8	27	22.3±3.8	6.9±6.1
Unimproved or worse	6	6.7±2.7	33	27.3±4.1	−20.6±4.9**
Total	89	100	121	100	—
Not gold-treated:					
Symptomless or markedly improved	40	26.5±3.6	14	16.5±4.0	10.0±5.4
Slightly improved	59	39.1±4.0	30	35.3±5.2	3.8±6.6
Unimproved or worse	52	34.4±3.9	41	48.2±5.4	−13.8±6.7
Total	151	100	85	100	—

Table 28. Immediate results after the last course of treatment in gold-treated and not gold-treated patients. Weighted means with regard to the duration of the disease, E.S.R. and the state of the joints at the beginning of the 1st course.

Immediate results	Gold-treated		Not gold-treated		Differences gold-treated − not gold-treated
	Number	Per cent	Number	Per cent	
Symptomless or markedly improved	264	67.2±2.4	82	28.9±2.7	38.3±3.6**
Slightly improved	100	25.4±2.2	116	40.8±2.9	−15.4±3.6**
Unimproved or worse	29	7.4±1.3	86	30.3±2.7	−22.9±3.0**
Total	393	100	284	100	—

It appears that complete remission of symptoms and marked improvement occurred more often among patients showing a poor response to previous treatment than among those who had relapsed following both gold and other therapy. Furthermore, aggravation was more frequent among those who had become worse between courses than among those whose improvement was inadequate. The respective differences are statistically significant or probable. The reason why cases which previously had been more or less intractable responded better to repeated treatment than relapsed cases is probably that the former had never

Table 29. Means of E.S.R. in gold-treated and not gold-treated men and women, given one or several courses of treatment, at the admission to the 1st course and at the discharge from the last one, and differences between the means.

Sex	Number of courses	E.S.R. at the first admission			E.S.R. at the last discharge			Differences
		Number	$M \pm \varepsilon(M)$	σ	Number	$M \pm \varepsilon(M)$	σ	
Gold-treated:								
Men	1 course . . .	112	26.9 ± 2.0	21.4	112	16.6 ± 1.7	18.1	$10.3 \pm 2.6^{**}$
	Several courses .	40	34.0 ± 3.2	20.0	40	26.4 ± 4.0	25.4	7.6 ± 5.1
	Total	152	28.8 ± 1.7	21.2	152	19.2 ± 1.7	20.6	$9.6 \pm 2.4^{**}$
Women	1 course . . .	233	33.8 ± 1.5	22.6	233	20.5 ± 1.2	18.2	$13.3 \pm 1.9^{**}$
	Several courses .	117	38.3 ± 2.1	22.9	117	27.6 ± 2.0	21.1	$10.7 \pm 2.9^{**}$
	Total	350	35.3 ± 1.2	22.8	350	22.9 ± 1.0	19.5	$12.4 \pm 1.6^{**}$
Not gold-treated:								
Men	1 course . . .	67	23.4 ± 2.9	23.6	67	16.4 ± 2.4	20.0	7.0 ± 3.8
	Several courses .	57	24.9 ± 2.8	21.1	57	16.5 ± 1.9	14.2	8.4 ± 3.4
	Total	124	24.1 ± 2.0	22.5	124	16.5 ± 1.6	17.6	$7.6 \pm 2.6^{*}$
Women	1 course . . .	108	28.8 ± 1.9	19.4	108	23.8 ± 1.7	17.4	5.0 ± 2.5
	Several courses .	98	31.0 ± 2.0	20.3	98	27.6 ± 2.1	20.9	3.4 ± 2.9
	Total	206	29.9 ± 1.4	19.8	206	25.6 ± 1.3	19.2	4.3 ± 1.9

been aggravated but instead often improved to some extent following preceding courses, whereas the latter actually had become worse, sometimes even much worse.

So far as the gold-treated patients are concerned the same thing is also illustrated by the E.S.R. changes occurring between courses. As will be seen from Table 27, those patients whose E.S.R. remained fairly constant between courses showed a better response to therapy than those whose E.S.R. increased during the corresponding period, the former group containing fewer unimproved or aggravated cases than the latter. The difference is statistically significant. While, as we have seen, the clinical aggravation taking place between courses in the gold-treated roughly agrees with the E.S.R. increase, there is no such parallellism for those not given gold. Clinical impairment was more frequent than rises in the E.S.R. among the latter. However, if among patients who were not treated with gold those whose E.S.R. remained fairly constant between courses are compared with those whose E.S.R. increased between courses, it will be found that both groups showed more or less the same response to treatment.

If, as was done for the immediate results after the first course of treatment, the response to the last course is weighted for gold and other therapy in all patients (Table 28), it again appears that gold is far more effective than other therapy. Thus the table shows that 67.2 ± 2.4 per cent of the gold-treated patients and only 28.9 ± 2.7 per cent of the patients not given gold became symptomless or

were considerably improved. The difference is not as marked now as for the comparison after one course only, for it is 38.3 ± 3.6 per cent as against 45.6 ± 3.5 per cent after the first course. The smaller difference must evidently be due to a less optimistic prognosis for those given several courses of treatment. Yet, even after the last course, the gold-treated patients showed far better results than those not receiving gold. Among the latter, moreover, there was a preponderance of such cases as were unimproved or aggravated following therapy. Nevertheless, just as after the first course, the patients not treated with gold included a higher percentage of slightly improved cases. The differences are statistically significant.

This chapter will be brought to a close with a survey of the E.S.R. changes taking place during the first course in those given one course only and between the beginning of the first and end of the last course in those given several courses. The patients were classified according to mode of treatment and sex (Table 29). In this connection it should be noted that the E.S.R. changes taking place during the first course which were discussed in the preceding chapter were considered regardless of subsequent courses.

The table shows that the E.S.R. tended to fall less after more courses. This agrees with the aforementioned tendency to poorer response to treatment after an increasing number of courses. What the table brings out most clearly, however, is that the E.S.R. falls much more in gold-treated than in other patients, both after one and more than one course. This is particularly true with regard to women. Gold-treated women thus showed statistically significant E.S.R. decreases after both one and more than one course. The corresponding difference is statistically significant for all gold-treated men too. But if one distinguishes between men given one course of gold therapy and men given several courses, only the first group proves to have a statistically significant difference. For patients not treated with gold there are no significant differences. In this connection it should be kept in mind that gold-treated patients had a somewhat higher E.S.R. than those not given gold. Among the former there was therefore more room for a decrease in the E.S.R., but this difference is not large enough adequately to explain the dissimilar results.

CHAPTER 5

MORTALITY

Before one analyzes the follow-up results it is interesting to estimate the mortality. Since those who die might chiefly be severely ill patients, the follow-up results could be more favourable than they actually are. Among the gold-treated patients 39 and among the others 7 had died when the follow-up study was undertaken, as was pointed out in the chapter on the character of the patients. By applying the death risks for the general population for the period 1941–45 to the patients observed, the figures given in the following table were obtained. These death risks are derived from a population so large that they can be regarded as having no standard errors. The standard error is consequently obtained by direct computation.

Observed and calculated number of deaths after the last course of treatment. Gold-treated and not gold-treated patients.

	Gold-treated		Not gold-treated	
	Men	Women	Men	Women
Observation time in years	905	1942	1010	1445
Observed number of deaths	15	24	6	1
Per cent	1.66	1.24	0.59	0.07
Calculated number of deaths	4.57	8.64	5.62	6.52
Per cent	0.50 ± 0.24	0.44 ± 0.15	0.56 ± 0.23	0.45 ± 0.18

The theoretical percentage of deaths is 0.50 ± 0.24 for men and 0.44 ± 0.15 for women in the gold-treated group. The actual death rates were much higher, namely 1.66 per cent for men and 1.24 per cent for women. For the gold-treated patients it is in other words a question of a statistically significant excess death rate of 0.5–1.0 per cent. Distributed over the more than 5 years long observation period, the excess mortality will be at most 0.18 per cent per annum. For the controls such was not the case: for them the figures agreed rather well, viz. 0.56 ± 0.23 per cent theoretical mortality as against 0.59 per cent observed mortality for men, with respectively 0.45 ± 0.18 per cent and 0.07 per cent for women.

For the sake of completeness it may here be remarked that 7 women died while they were actually receiving gold treatment. (Their first course had been given in the years 1939–44.) The immediate causes of death will be found in Table 30. One of these deaths can with some degree of certainty be attributed

Table 30. Deaths during gold therapy.

Age, years	At beginning of first course		Duration, years	Cause of death
	Joint status, no. of plus	E.S.R.		
37	10	58	2.5	Bronchopneumonia
48	9	36	2.3	Encephalitis
43	19	106	1.1	Thrombopenia + Purpura
29	10	35	5.5	Bronchopneumonia
27	12	27	1.1	Bronchopneumonia
54	23	59	3.1	Panmyelophthisis + Haemorrhagia cerebri
46	9	30	0.4	Thyreotoxicosis + Myodegeneratio cordis

to the gold treatment, namely that caused by thrombopenic purpura. Not unlikely the death caused by encephalitis and that by panmyelophthisis were also due to the gold treatment. No reliable data are available regarding patients that might have died in the course of ordinary physical therapy. Hence the two treatments cannot be compared in this respect.

Clearly the excess mortality for those receiving gold therapy could be due to the gold, or to the severity of their rheumatoid arthritis, or to a combination of both. The causes of death among the gold-treated patients and in the control series are given in Table 31, the required data being supplied by the local authorities concerned. Such information obviously cannot always be precise enough to allow exact determination of the immediate cause of death.

On the part of 5 gold-treated patients, for example, the cause of death is merely given as rheumatoid arthritis or rheumatism. In such cases one cannot establish the immediate cause of death, and the question whether gold therapy was a causative or contributory factor must be left unanswered. One of these patients died 0.7 years and the others 1.0 years or longer after the last course of treatment. It should be noted that all these patients had severe rheumatoid arthritis with considerable joint involvement and high E.S.R. at the beginning of the first course.

Other 6 gold-treated patients died of malignant tumours, 2 of cerebral vascular catastrophes, 1 of cardiosclerosis, 2 of biliary tract diseases, 1 of hepatic cirrhosis, 2 of pulmonary tuberculosis, and for one patient psychosis is given as the cause of death. It is extremely unlikely, and impossible to establish, that the cause of death bore any relation to the treatment given or to the basic disease in any of these cases.

Among the gold-treated patients a total of 9 deaths were caused by various cardiac affections, valvular defect, endocarditis, myocarditis and pericarditis. In such cases it is reasonable to suspect that the underlying factor is the rheumatic disease. And a diagnosis of chronic myocarditis (3 cases) may be disguised cardiosclerosis. Here it is worth noting that 2 of the 7 deaths among the controls were due to heart failure.

Table 31. Causes of death.

	Number of deaths	Interval between end of treatment and death, in years
Causes of death in cases treated with gold:		
Vitium cordis	4	1.2 1.8 3.4 9.2
Endocarditis ulcerosa	1	8.1
Pericarditis	1	2.8
Myocarditis chronica	3	0.2 2.3 4.0
Cardiosclerosis	1	2.2
Pneumonia, bronchopneumonia	5	0.7 2.7 3.2 3.7 5.5
Tuberculosis pulmonum	2	2.1 3.2
Nephritis chronica, renal disease, uraemia	3	2.4 5.5 8.6
Thrombopenia, purpura	2	0.2 0.5
Cholelithiasis, cholecystitis	2	3.2 3.4
Cirrhosis hepatis	1	2.2
Haemorrhagia cerebri, cerebral infarct	2	2.8 2.8
Malignant tumor	6	0.4 0.4 0.4 1.0 2.7 10.0
Psychosis	1	1.7
Rheumatoid arthritis, rheumatism	5	0.7 1.0 1.1 2.8 3.8
Causes of death in cases not treated with gold:		
Vitium cordis	2	2.8 5.1
Nephritis chronica, renal diseases	2	2.3 5.1
Haemorrhagia cerebri	1	4.8
Malignant tumor	1	6.1
Accident	1	6.9

Fatal pneumonia or bronchopneumonia occurred in 5 gold-treated cases. These conditions are known to be included among the commonest causes of death in rheumatoid arthritis, mainly because of the impaired general status etc. associated with rheumatoid arthritis.

Renal diseases are given as the cause of death for 3 of the gold cases. It is known that gold can induce a nephrosis-like affection which, however, usually is transient. Moreover these deaths occurred as long as 2.4, 5.5, and 8.6 years after treatment with gold. Nor it is impossible that these renal disorders were due to the basic disease. For several authors have pointed out that rheumatoid arthritis can lead to amyloidosis. Account should here be taken of the fact that renal diseases caused 2 of the 7 deaths among the controls.

Finally 2 of those receiving gold died of thrombopenia or purpura as soon as 0.2 and 0.5 years after therapy. Even though conclusive evidence is lacking it seems probable that these deaths were secondary to the gold therapy.

As noted 2 of the 7 deaths among the controls were due to renal disease and 2 to organic heart disease. The remaining 3 died of cerebral haemorrhage, malignant tumour and by misadventure.

An analysis of the severity of the rheumatic disorder in the cases of death reveals that patients given gold on the whole had severe disease. Thus 21 of the 39 gold-treated patients who died displayed severe joint symptoms (more than 12 +), 25 had E.S.R. levels over 40 mm. and 15 had been ill more than 3 years at the beginning of the first course of therapy. Similarly, at the beginning of the first couse of therapy, 5 of the 7 controls who died had moderately severe joint symptoms (8–12 +). 3 had E.S.R. levels exceeding 40 mm and only one had been ill more than 3 years. Thus, among those who died, it would seem that the average severity of rheumatoid arthritis was lower in the controls than in the patients given gold. However, the data do not warrant any conclusions.

In sum, amounting to 1 per cent at most, the excess mortality of the gold-treated patients could be due to their having the disease more severely than the controls. Yet this explanation does not fully seem to meet the case: the gold treatment could be responsible for part of the excess mortality. If so, however, the available data do not permit any estimation of what proportion of the excess mortality was due to gold. Nevertheless it is worth noting that, as mentioned, Sundelin (1948) in a larger series found an excess death rate due to gold of 0.36 per cent.

Lastly, considering that the excess deaths occurred among those gold-treated patients who were most severely ill, the number of deaths was too small to affect materially the results of the follow-up examination.

CHAPTER 6

END RESULTS

The crucial problem is whether the effects of gold therapy are lasting. In order to assemble data on which to base an opinion the patients, both gold-treated and controls, were sent a questionary (for full details see Chapter 2). It should be borne in mind that this follow-up study involved no clinical examination and was concerned merely with answers to a circularized questionary, answers occasionally obtained only after mediation of the local Pensions Board. As the patients concerned had their homes in all parts of Sweden clinical examinations, however desirable, would have been impractical if not impossible. Another point worth reiterating is that any errors should affect the gold-treated patients and the control patients in an equal degree and would therefore tend to cancel out when the two groups are compared.

Before the results of the follow-up study can be discussed it is necessary to explain how the patients' replies were classified and evaluated. The patients were asked whether, at the time of replying, they were doing well, much better, slightly better, unchanged or worse than they were when discharged from hospital after the last course of treatment. (See Fig. 1 in Chapter 2.) The late results were then obtained by relating the patient's reply to his condition at the beginning of the first course of therapy.

A number of the ex-patients in addition to the bare answers requested gave detailed information enabling direct comparisons to be made with their condition at the beginning of the first course of treatment. Some patients' remarks on their working capacity included information which made it easier to evaluate their health status. The bare answers to questions were, whenever unsupplemented by other information, interpreted as set out in the scheme below.

Relative changes in health status from the beginning of the first course to end of the last (i), from the end of the last course to the follow-up examination (ii), and from the beginning of the first course to the follow-up examination (iii).

(i)	(ii)	(iii)
symptomless	unchanged	symptomless
symptomless	well	symptomless
symptomless	much better	markedly improved
symptomless	slightly better	slightly improved
symptomless	worse	relapsed

(i)	(ii)	(iii)
markedly improved	well	symptomless
markedly improved	unchanged	markedly improved
markedly improved	much better	markedly improved
markedly improved	slightly better	markedly improved
markedly improved	worse	relapsed
slightly improved	well	symptomless
slightly improved	much better	markedly improved
slightly improved	unchanged	slightly improved
slightly improved	slightly better	slightly improved
slightly improved	worse	relapsed
unchanged	well	symptomless
unchanged	much better	markedly improved
unchanged	slightly better	slightly improved
unchanged	unchanged	unimproved
unchanged	worse	worse
worse	well	symptomless
worse	much better	markedly improved
worse	slightly better	slightly improved
worse	unchanged	worse
worse	worse	worse

The interpretation of the answers (see scheme) was for the most part conducted along obvious lines and requires little comment. Here it will suffice to mention that it often was difficult to tell how much worse those were who said they were worse. They were simply classified as relapsed. This category, then, comprises cases showing improvement in conjunction with therapy, or very soon after for a few patients submitting information to that effect, and aggravation at the time of the follow-up study. How long such patients had been worse, and whether they were worse than at the beginning of the first course of treatment, are questions upon which we can only speculate. Those stated to be unimproved or worse than at the beginning of the first course according to available data definitely were unimproved or worse. The relationships between the immediate response to therapy and the follow-up results are discussed in another section of this chapter (cf. Table 39).

In Table 32 are compared the state of health at the time of the follow-up study and the state of health at the beginning of the first course of treatment. The table shows that a greater proportion of the gold-treated patients than of the other patients were symptomless at the time of the follow-up, namely 14.9 and 6.6 per cent respectively. The difference is statistically significant. The proportion of markedly improved patients was statistically about the same in the two groups, but the aggregated difference between the symptomless and markedly improved patients in the two groups becomes 16.2 ± 3.4 per cent, which attains the level of statistical significance. Relapsed cases—where improvement

Table 32. End results in gold-treated and not gold-treated patients.

End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Symptomless	75	14.9±1.6	24	6.6±1.3	8.3±2.1**
Markedly improved . . .	205	40.8±2.2	119	32.9±2.5	7.9±3.3
Slightly improved	67	13.3±1.5	84	23.2±2.2	– 9.9±2.7**
Relapsed	133	26.5±2.0	67	18.5±2.0	8.0±2.8*
Unimproved	14	2.8±0.7	28	7.7±1.4	– 4.9±1.6**
Worse	8	1.6±0.6	40	11.0±1.6	– 9.4±1.7**
Total	502	100	362	100	—

may have been present for a varying length of time before the disease aggravated once more—were proportionately more numerous amongst the gold-treated patients (20.5 per cent) than among patients not given gold (18.5 per cent), the difference being statistically probable. Relatively fewer of the slightly improved patients and also of those classified as unimproved and worse had been receiving gold. The differences are significant.

As noted at the beginning of this chapter, we know with regard to those patients who were aggregated in the group headed "relapsed" that their condition at the time of the follow-up study was worse than immediately following treatment but we lack definite evidence as to whether they were better or worse than at the beginning of treatment. However, from the available data some additional information may be deduced. Thus the group comprised 4.5 ± 1.8 per cent of gold-treated patients and nil per cent of controls who were recorded as being symptomless immediately after treatment. Further it included 66.9 ± 4.1 per cent of gold-treated patients and 38.8 ± 6.0 per cent of controls who were classified as markedly improved immediately after the course of treatment. (The difference between these two frequencies, 28.1 ± 7.3 per cent, is statistically significant.) Lastly it contained 28.6 ± 3.9 per cent of gold-treated cases and 61.2 ± 6.0 per cent of control cases where slight improvement was the immediate result of the treatment given. (The difference, —32.6 ± 7.2 per cent, is statistically significant.) Evidently, therefore, these relapses cannot have influenced those cases which were considered symptomless or markedly improved at the follow-up investigation. On the other hand, it is possible that many of those showing marked improvement immediately after treatment had undergone an aggravation but not become as ill as they were before therapy was instituted. Here it should be noted that this group included a significantly greater number of gold-treated patients than of controls. Most likely, therefore, the group of slightly improved gold-treated cases should if anything be larger. Those cases which were slightly improved immediately after therapy and later were classified as aggravated could of course affect only those groups which at the follow-up investigation were regarded as unimproved or aggravated. As the relapsed

Table 33. End results in gold-treated and not gold-treated men and women.

End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Men:					
Symptomless	29	19.1±3.2	11	7.4±2.2	11.7±3.9**
Markedly improved	67	44.1±4.0	56	37.8±4.0	6.3±5.7
Slightly improved	27	17.8±3.1	32	21.6±3.4	– 3.8±4.6
Relapsed	24	15.8±3.0	26	17.6±3.1	– 1.8±4.3
Unimproved	2	1.3±0.9	9	6.1±2.0	– 4.8±2.2
Worse	3	2.0±1.1	14	9.5±2.4	– 7.5±2.6*
Total	152	100	148	100	—
Women:					
Symptomless	46	13.1±1.8	13	6.1±1.6	7.0±2.4*
Markedly improved	138	39.4±2.6	63	29.4±3.1	10.0±4.0*
Slightly improved	40	11.4±1.7	52	24.3±2.9	–12.9±3.4**
Relapsed	109	31.1±2.5	41	19.2±2.8	11.9±3.8**
Unimproved	12	3.4±1.0	19	8.9±1.9	– 5.5±2.1*
Worse	5	1.4±0.6	26	12.1±2.2	–10.7±2.3**
Total	350	100	214	100	—

group included a significantly larger proportion of controls than of gold-treated cases which had been slightly improved immediately after treatment, it seems most likely that such an increment mainly would be added to the unimproved or aggravated control groups.

When men and women were compared with respect to the follow-up results (Table 33), it appeared that a significantly greater percentage of symptomless men had had gold, but that the corresponding difference for women only was statistically probable (7.0 ± 2.4 per cent). The gold-treated women showed marked improvement oftener than those not given gold, the difference between the respective percentages—39.4 and 29.4—being probable. There seemed to be relatively fewer worse cases among the men in the gold-treated group (2.0 per cent) than among the other men (9.5 per cent); the difference is statistically probable. The corresponding difference with respect to women is greater, i.e. 10.7 ± 2.3 per cent which is statistically significant, perhaps because the women were more numerous. The category of relapsed women was greater in the gold series (31.1 per cent) than in the non-gold series (19.2 per cent.) This difference is also statistically significant. These deviations found by a comparison of men and women may have to do with the fact established in a preceding chapter that rheumatoid arthritis tends to be of differing severity in men and in women.

The follow-up results show that among women relapses evidently were more frequent following gold therapy than in the controls. Still the percentage of symptomless patients given gold treatment exceeded the proportion of symp-

Table 34. End results in gold-treated and not gold-treated patients, distributed according to E.S.R. at the admission.

End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
E.S.R. = < 20:					
Symptomless	36	23.5 ± 3.4	10	6.2 ± 1.9	17.3 ± 3.9**
Markedly improved	68	44.4 ± 4.0	61	37.7 ± 3.8	6.7 ± 5.5
Slightly improved	24	15.7 ± 2.9	40	24.7 ± 3.4	– 9.0 ± 4.5
Relapsed	21	13.7 ± 2.8	30	18.5 ± 3.1	– 4.8 ± 4.2
Unimproved	3	2.0 ± 1.1	9	5.6 ± 1.8	– 3.6 ± 2.1
Worse	1	0.7 ± 0.7	12	7.4 ± 2.1	– 6.7 ± 2.2**
Total	153	100	162	100	—
E.S.R. = 20–39:					
Symptomless	22	11.3 ± 2.3	9	7.6 ± 2.4	3.7 ± 3.3
Markedly improved	83	42.6 ± 3.5	32	26.9 ± 4.1	15.7 ± 5.4*
Slightly improved	20	10.3 ± 2.2	29	24.4 ± 3.9	– 14.1 ± 4.5**
Relapsed	61	31.3 ± 3.3	23	19.3 ± 3.6	12.0 ± 4.9
Unimproved	5	2.6 ± 1.1	10	8.4 ± 2.5	– 5.8 ± 2.7
Worse	4	2.1 ± 1.0	16	13.4 ± 3.1	– 11.3 ± 3.3**
Total	195	100	119	100	—
E.S.R. = 40–ω:					
Symptomless	17	11.0 ± 2.5	5	6.2 ± 2.7	4.8 ± 3.7
Markedly improved	54	35.1 ± 3.8	26	32.1 ± 5.2	3.0 ± 6.4
Slightly improved	23	14.9 ± 2.9	15	18.5 ± 4.3	– 3.6 ± 5.2
Relapsed	51	33.1 ± 3.8	14	17.3 ± 4.2	15.8 ± 5.7*
Unimproved	6	3.9 ± 1.6	9	11.1 ± 3.5	– 7.2 ± 3.8
Worse	3	1.9 ± 1.1	12	14.8 ± 3.9	– 12.9 ± 4.1**
Total	154	100	81	100	—

tomless controls; and, among women, gold treatment probably gave rise to marked improvement more often than other treatment. Conversely the controls oftener showed slight improvement or were definitely unchanged or worse relative to the beginning of the first course than the patients receiving gold treatment.

It will be remembered that the immediate results of therapy were assessed from changes in 3 factors which, by assumption (see motivation in preceding chapter), were considered characteristic of the nature of the disease, viz. sedimentation rate, joint status and duration of the disease. Consequently the follow-up results will similarly be analyzed with respect to the state of these 3 factors at the beginning of the first course of therapy.

A comparison of the follow-up results and the E.S.R. elevation displayed by the patients at the beginning of the first course is made in Table 34. As before the cases were divided into 3 groups of E.S.R. elevation.

Table 35. End results in gold-treated and not gold-treated patients, distributed according to the state of the joints at the admission.

End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
State of the joints = < 8 plus:					
Symptomless	42	22.0±3.0	9	9.8±3.1	12.2±4.3*
Markedly improved	92	48.2±3.6	30	32.6±4.9	15.6±6.1*
Slightly improved	25	13.1±2.4	21	22.8±4.4	– 9.7±5.0
Relapsed	27	14.1±2.5	15	16.3±3.9	– 2.2±4.6
Unimproved	3	1.6±0.9	7	7.6±2.8	– 6.0±2.9
Worse	2	1.0±0.7	10	10.9±3.2	– 9.9±3.3**
Total	191	100	92	100	—
State of the joints = 8–12 plus:					
Symptomless	27	14.4±2.6	11	8.9±2.6	5.5±3.7
Markedly improved	67	35.8±3.5	44	35.8±4.3	0
Slightly improved	22	11.8±2.4	29	23.6±3.8	–11.8±4.5*
Relapsed	64	34.2±3.5	20	16.3±3.3	17.9±4.8**
Unimproved	4	2.1±1.0	9	7.3±2.3	– 5.2±2.5
Worse	3	1.6±0.9	10	8.1±2.5	– 6.5±2.7
Total	187	100	123	100	—
State of the joints = 13 plus or more:					
Symptomless	6	4.8±1.9	4	2.7±1.3	2.1±2.3
Markedly improved	46	37.1±4.3	45	30.6±3.8	6.5±5.7
Slightly improved	20	16.1±3.3	34	23.1±3.5	– 7.0±4.8
Relapsed	42	33.9±4.3	32	21.8±3.4	12.1±5.5
Unimproved	7	5.6±2.1	12	8.2±2.3	– 2.6±3.1
Worse	3	2.4±1.4	20	13.6±2.8	–11.2±3.1**
Total	124	100	147	100	—

Among patients with a low sedimentation rate (below 20 mm) before treatment those given gold showed a higher frequency of symptomless cases at the follow-up than those not given gold. The difference amounts to 17.3 ± 3.9 per cent and is statistically significant. Symptomless patients whose initial E.S.R. lay between 20 and 39 mm showed much the same condition at the follow-up whether they had been given gold or not. But in this E.S.R. group those given gold seemed to be markedly improved oftener than the others. The statistically probable difference is 15.7 ± 5.4 per cent.

Those with an E.S.R. of 40 mm or more prior to treatment displayed no marked differences with respect to freedom from symptoms or improvement following gold or other therapy. The relapsed group, however, contained a majority of gold-treated cases. The difference is 15.8 ± 5.7 per cent and statistically probable. In all E.S.R. groups aggravation was more common among patients not receiving gold. Thus, in groups of increasing E.S.R. elevation,

Table 36. End results in gold-treated and not gold-treated patients, distributed according to the number of plus per affected joint at the admission.

Number of plus per affected joint	End results	Gold-treated		Not gold-treated		Differences gold treated – not gold-treated
		Number	Per cent	Number	Per cent	
1.0–1.1	Symptomless	32	24.2±3.7	15	10.4±2.5	13.8±4.5**
	Markedly improved	63	47.7±4.3	55	38.2±4.0	9.5±5.9
	Slightly improved	12	9.1±2.5	33	22.9±3.5	−13.8±4.3**
	Relapsed	24	18.2±3.4	23	16.0±3.1	2.2
	Unimproved or worse	1	0.8±0.8	18	12.5±2.8	−11.7±2.9**
	Total	132	100	144	100	—
1.2–1.4	Symptomless	18	10.9±2.4	2	1.6±1.1	9.3±2.6**
	Markedly improved	64	38.8±3.8	35	28.5±4.1	10.3±5.6
	Slightly improved	23	13.9±2.7	34	27.6±4.0	−13.7±4.8*
	Relapsed	47	28.5±3.5	21	17.1±3.4	11.4±4.9
	Unimproved or worse	13	7.9±2.1	31	25.2±3.9	−17.3±4.4**
	Total	165	100	123	100	—
1.5–ω	Symptomless	25	12.2±2.3	7	7.4±2.7	4.8
	Markedly improved	78	38.0±3.4	29	30.5±4.7	7.5
	Slightly improved	32	15.6±2.5	17	17.9±3.9	−2.3
	Relapsed	62	30.2±3.2	23	24.2±4.4	6.0
	Unimproved or worse	8	3.9±1.4	19	20.0±4.1	−16.1±4.3**
	Total	205	100	95	100	—

aggravation occurred in 0.7, 2.1, and 1.9 per cent of the gold-treated patients and in 7.4, 13.4, and 14.8 per cent of those not given gold. The differences between the respective pairs are statistically significant.

Thus gold treatment seems to have better results over the long view, both for low and high E.S.R. values at the beginning of treatment, i.e. whether the rheumatic process is of high or of low activity. For, a higher proportion of those patients that were not given gold became worse than of those receiving gold. The difference seems particularly marked in the groups with low or moderately high E.S.R. levels prior to treatment, because a larger percentage of gold-treated patients in these groups proved symptomless or markedly improved at the follow-up.

For the purposes of relating the joint status at the beginning of the first course of treatment to the end results, the patients were as before divided into 3 groups according to the total number of plus signs per patient (Table 35).

A comparison of the long-term effects of gold treatment and physical therapy reveals that patients with both mild and severe joint symptoms became worse less often if they had been given gold than if they had received other therapy. Among gold-treated patients with mild joint symptoms 1.0 per cent and among

Table 37. End results in gold-treated and not gold-treated patients, distributed according to the duration of the disease.

End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Duration = < 1 year:					
Symptomless	30	23.4 ± 3.7	13	9.1 ± 2.4	14.3 ± 4.4**
Markedly improved	55	43.0 ± 4.4	56	39.2 ± 4.1	3.8 ± 6.0
Slightly improved	15	11.7 ± 2.8	31	21.7 ± 3.4	−10.0 ± 4.4
Relapsed	24	18.8 ± 3.5	26	18.2 ± 3.2	0.6 ± 4.7
Unimproved	1	0.8 ± 0.8	9	6.3 ± 2.0	− 5.5 ± 2.2*
Worse	3	2.3 ± 1.3	8	5.6 ± 1.9	− 3.3 ± 2.3
Total	128	100	143	100	—
Duration = 1.0–2.9 years:					
Symptomless	19	11.9 ± 2.6	5	4.8 ± 2.1	7.1 ± 3.3
Markedly improved	63	39.6 ± 3.9	29	27.6 ± 4.4	12.0 ± 5.9
Slightly improved	20	12.6 ± 2.6	32	30.5 ± 4.5	−17.9 ± 5.2**
Relapsed	50	31.4 ± 3.7	17	16.2 ± 3.6	15.2 ± 5.2*
Unimproved	6	3.8 ± 1.5	8	7.6 ± 2.6	− 3.8 ± 3.0
Worse	1	0.6 ± 0.6	14	13.3 ± 3.3	−12.7 ± 3.4**
Total	159	100	105	100	—
Duration = 3.0 years or more:					
Symptomless	26	12.1 ± 2.2	6	5.3 ± 2.1	6.8 ± 3.0
Markedly improved	87	40.5 ± 3.3	34	29.8 ± 4.3	10.7 ± 5.4
Slightly improved	32	14.9 ± 2.4	21	18.4 ± 3.6	− 3.5 ± 4.3
Relapsed	59	27.4 ± 3.0	24	21.1 ± 3.8	6.3 ± 4.8
Unimproved	7	3.3 ± 1.2	11	9.6 ± 2.8	− 6.3 ± 3.0
Worse	4	1.9 ± 0.9	18	15.8 ± 3.4	−13.9 ± 3.5**
Total	215	100	114	100	—

those not given gold 10.9 per cent became worse. The corresponding figures for those with severe joint involvement are 2.4 and 13.6 per cent; and the respective differences are statistically significant.

It seems, too, that a larger percentage of the gold-treated patients with mild joint symptoms became symptomless or markedly improved than of the corresponding group of the other patients. Symptomless at the follow-up were 22.0 per cent of the former and 9.8 per cent of the latter; whereas 48.2 and 32.6 per cent respectively were markedly improved. The differences are statistically probable. The aggregate figures for symptomless and markedly improved patients in the two groups are 70.2 and 42.4 per cent, which are statistically different by a significant amount (27.8 ± 6.2 per cent).

It is interesting to note, too, that among patients with moderately severe joint involvement those in the relapsed category more often had received gold

than other therapy, namely 34.2 per cent as against 16.3 per cent. The difference is statistically significant.

As before, the foregoing joint status classification by the number of plus per person will now be supplemented by a similar division into 3 groups with respect to the number of plus per affected joint.

Table 36 shows that the results are now again more favourable for those given gold treatment. Thus the gold-treated cases with mild or moderately severe joint changes according to this basis for classification included a higher proportion of symptomless patients than the group not given gold. In addition, at the follow-up a larger percentage of those not given gold were unchanged or worse, but slight improvement proved more common among those not given gold, particularly if their joint symptoms had been mild from the beginning. The differences in question are statistically significant or probable.

On the whole, therefore, the long-term results of gold therapy seemed rather better than those of physiotherapy regardless of the severity of the joint symptoms. For among both mild and severe cases a larger percentage of those not receiving gold were unimproved or aggravated. Yet the late results of gold treatment probably were particularly good in cases with mildly affected joints: in this group those given gold included a larger proportion of symptomless or markedly improved patients at the follow-up.

Lastly the effects of the duration of the disease on the nature of the late results will be considered. Table 37 discloses the relationship between the follow-up results and the duration of the disease from the onset to the first course of treatment. Three groups of disease duration are used, just as before. It will be seen that gold treatment apparently had better follow-up results than other therapy whether the disease was of long or of short duration. Among patients symptomless at the follow-up who had been ill for less than a year before the first course of treatment there were 23.4 per cent of the gold-treated group and only 9.1 per cent of the other group. This difference is statistically significant. Moreover, a larger proportion of those not given gold than of those receiving gold in this group seemed unchanged, viz. 0.3 and 0.8 per cent. This difference is statistically probable. When the duration was 1–2.9 years relapses seemed more numerous following gold therapy. The figures are 31.4 and 16.2 per cent and their difference is statistically probable. This group also included a higher percentage of aggravations among those not given gold than among those so treated, viz. 13.3 and 0.6; the difference between these figures is statistically significant. Aggravation was also commoner among those not given gold with a duration exceeding 3 years, the respective percentages being 15.8 and 1.9 and differing significantly.

It seems, thus, that gold therapy has long-term results superior to those of other treatment, particularly when treatment commences soon after the onset of the disease. Then a higher proportion of those given gold were symptomless at the follow-up. But one cannot avoid the impression that gold treatment had better follow-up results after longer durations as well. For those not given gold

Table 38. End results in gold-treated and not gold-treated patients. Weighted means with regard to the duration of the disease, E.S.R. and the state of the joints at the admission.

End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
	Number	Per cent	Number	Per cent	
Symptomless or markedly improved	217	55.2±2.5	108	38.0±2.9	17.2±3.8**
Slightly improved	51	13.0±1.7	64	22.5±2.5	− 9.5±3.0**
Relapsed	108	27.5±2.3	53	18.7±2.3	8.8±3.3*
Unimproved or worse	17	4.3±1.0	59	20.8±2.4	−16.5±2.6**
Total	393	100	284	100	—

whose disease was of moderately long or long duration were more often worse at the follow-up than those who had been treated with gold.

The foregoing follow-up results of gold therapy and of other therapy are, as noted in the chapter on the immediate results of therapy (Table 17), somewhat incompatible, particularly as regards the E.S.R., joint status and duration. Gold-treated cases generally were more severe than those treated otherwise. Consequently the groups have been weighted to have equal representation in the two series (Table 38).

However, the weighted numbers in this table indicate no appreciable deviations from the original table of all the follow-up results. Symptomless and markedly improved cases were markedly more frequent among gold-treated patients (55.2 per cent) than among the other patients (38.0 per cent). The statistically significant difference is 17.2 ± 3.8 per cent. Relapse occurred in 27.5 per cent of the gold-treated patients and in 18.7 per cent of the other patients, the difference between the two being probable.

A larger percentage of those not given gold became slightly improved or unimproved or worse. The respective percentage are 22.5 and 20.8, as against 13.0 and 4.3 per cent among the gold-treated cases. The differences are statistically significant.

The problem of comparing immediate and late results of gold treatment now presents itself. As noted, it was possible to follow up altogether 502 of 573 patients registered as having been given gold treatment, i.e. 87.6 per cent. Of the remaining 71 persons some had died, some could not be traced, and some returned useless data.

Table 39 shows how the results of gold therapy and of other treatment immediately after last course of treatment compare with those at the follow-up. For this purpose the patients were divided into those that had had one course and those that had more than one course of treatment, the immediate results for the latter being those after the most recent course of therapy.

Table 39. Percentual distribution according to the end results in gold-treated and not gold-treated patients given one or several courses of treatment, grouped according to the immediate result after the last course.

Number of courses	Immediate results after the last course	Number of cases	End results: Symptomless		Markedly improved		Slightly improved		Relapsed		Unimproved		Worse	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
One course	Symptomless	35	19	54.3	10	28.6	—	—	6	17.1	—	—	—	—
	Markedly improved	210	28	13.3	119	56.7	6	2.9	56	26.7	1	0.5	—	—
	Slightly improved	90	14	15.6	21	23.3	36	40.0	18	20.0	1	1.1	—	—
	Unimproved	10	2	20.0	1	10.0	3	30.0	—	—	2	20.0	2	20.0
	Worse	—	—	—	—	—	—	—	—	—	—	—	—	—
	Total	345	63	18.3	151	43.8	45	13.0	80	23.2	4	1.2	2	0.6
Several courses	Symptomless	1	—	—	1	100.0	—	—	—	—	—	—	—	—
	Markedly improved	92	11	12.0	43	46.7	5	5.4	29	31.5	4	4.3	—	—
	Slightly improved	39	1	2.6	5	12.8	11	28.2	18	46.2	3	7.7	1	2.6
	Unimproved	17	—	—	5	29.4	2	11.8	4	23.5	2	11.8	4	23.5
	Worse	8	—	—	—	—	4	50.0	2	25.0	1	12.5	1	12.5
	Total	157	12	7.6	54	34.4	22	14.0	53	33.8	10	6.4	6	3.8
One course	Symptomless	8	2	25.0	3	37.5	3	37.5	—	—	—	—	—	—
	Markedly improved	69	9	13.0	41	59.4	6	8.7	12	17.4	1	1.4	—	—
	Slightly improved	80	6	7.5	26	32.5	25	31.3	19	23.8	4	5.0	—	—
	Unimproved	42	—	—	7	16.7	9	21.4	—	—	5	11.9	21	50.0
	Worse	—	—	—	—	—	—	—	—	—	—	—	—	—
	Total	199	17	8.5	77	38.7	43	21.6	31	15.6	10	5.0	21	10.6
Several courses	Symptomless	2	2	100.0	—	—	—	—	—	—	—	—	—	—
	Markedly improved	38	1	2.6	21	55.3	6	15.8	10	26.3	—	—	—	—
	Slightly improved	61	3	4.9	15	24.6	22	36.1	18	29.5	3	4.9	—	—
	Unimproved	35	1	2.9	5	14.3	8	22.9	6	17.1	7	20.0	8	22.9
	Worse	27	—	—	1	3.7	5	18.5	2	7.4	8	29.6	11	40.7
	Total	163	7	4.3	42	25.8	41	25.2	36	22.1	18	11.0	19	11.7

The table shows that among the 245 patients who became symptomless or markedly improved after a single course of gold 176 were considered symptomless or markedly improved at the follow-up, in other words 71.8 per cent. And, weeding out the markedly improved cases, one finds that 19 of the 35 that became symptomless after a single gold course still were symptomless at the follow-up (54.3 per cent) and 10 were markedly improved (28.6 per cent). These

figures suggest that a large proportion of recoveries and marked improvements after a single course of gold therapy are of lasting character. It is worth noting also that of the 93 patients who were symptomless or markedly improved immediately after several gold courses 55 (59.1 per cent) were markedly improved or symptomless at the follow-up.

It is more surprising that several of those who became neither symptomless nor markedly improved but were unchanged after a single gold course had become symptomless or markedly improved at the follow-up. Thus, of 10 patients who were unchanged after a single course of gold 3 (30.0 per cent) proved symptomless or markedly improved at the follow-up, and of 25 unchanged or aggravated after several gold courses 5 (20.0 per cent) were symptomless or considerably improved when the follow-up was done.

Evidently, thus, considerable improvement can follow even some time after the end of gold treatment. Obviously one cannot tell whether such improvement is dependent on a spontaneous remission of the disease or is due to a delayed effect of the gold treatment. But many reports suggest that the action of gold can set in many months after cessation of gold therapy.

To shed more light on the matter it was investigated to what extent improvement was lasting among patients not given gold (Table 39). Among those receiving only one course of treatment, this produced 77 symptomless or markedly improved cases and 55 of these were symptomless or markedly improved at the follow-up, i.e. 71.4 per cent or approximately the same proportion as in the gold-treated series. Of the 8 that became symptomless after treatment 2 were symptomless and 3 markedly improved at the follow-up, i.e. 62.5 per cent. This figure is lower than for the gold-treated patients, but the patients were too few to warrant any conclusions. Of those receiving more than one course 40 became symptomless or markedly improved and altogether 60.0 per cent of these were symptomless or markedly improved at the follow-up, i.e. about the same proportion as of the gold-treated patients that had been given more than one course.

As for the gold-treated patients, one finds among those not given gold some showing no immediate response to therapy who were symptomless or markedly improved at the time of the follow-up. For example, among 42 who were unimproved after a single course of physical therapy 7 (16.7 per cent) showed marked improvement at the follow-up. Of those given more than one course 62 were unimproved or worse after therapy, but at the follow-up 1 of them was symptomless and 6 were markedly improved (total: 11.3 per cent).

A certain number of remissions evidently occur after physical therapy too. But, as in the case of gold-treated patients, one obviously has no way of telling whether spontaneous remission of the disease or a delayed therapeutic effect was responsible. The figures nevertheless suggest that such delayed improvements are less frequent after physiotherapy than after gold treatment.

The question now arises as to the incidence of aggravation following treatment. Table 39 reveals that a larger percentage of those that were symptomless

or markedly improved immediately after gold therapy were worse at follow-up than of the corresponding patients in the other series. Thus the relapsed group includes 25.3 per cent of those who were symptomless or markedly improved after a single course and 31.2 per cent of those given repeated courses of gold. The corresponding figures for those not given gold are 15.6 and 25.0 per cent.

Yet, as noted, it was difficult from the follow-up results to estimate the degree of aggravation. For a small number of cases only it was possible to say definitely that at follow-up the patient in question was aggravated or unchanged compared with his condition at the beginning of the first course of treatment. Ten patients given one course of gold treatment and 25 patients given more than one such course became unchanged or worse in response to therapy. At follow-up 4 of the former and 8 of the latter (respectively 40.0 and 32.0 per cent) were still considered unchanged or worse. After a single course of physical therapy 42 and after repeated courses 62 patients were unchanged or worse; and at follow-up 26 of the former (61.9 per cent) and 34 of the latter (54.8 per cent) proved unchanged or worse. In addition, at follow-up aggravation was reported by 20.0 per cent of those gold-treated and by 50.0 per cent of those not gold-treated patients who had shown no response to a single course of treatment. This would seem to indicate that patients not treated with gold became worse rather oftener. However, the percentages are from statistical points of view neither significantly nor probably different. But when one combines the results for all courses one finds that 12 of 35 (34.3 per cent) gold-treated and 60 of 104 (57.7 per cent) physically treated patients were unimproved or worse at follow-up. And the difference, 23.4 ± 9.3 per cent, is here statistically probable.

The point is now reached where it becomes necessary to ascertain the effects of a variety of factors on the long-term results. In the first place it is apparent, as Table 40 illustrates, that the follow-up results as well as the immediate responses to therapy tended to be less favourable with increasing number of courses. A larger proportion of the patients receiving one gold course only became, thus, symptomless or improved greatly than of those given two such courses; and a higher percentage of the latter were unimproved or worse. The first difference is statistically significant, the second probable.

The difference is not so appreciable for patients treated otherwise than with gold. A statistically probable difference nevertheless exists between those made symptomless or improved markedly by one and by two courses. It is worth repeating in this connection that on the whole those given repeated courses had rheumatoid arthritis more severely in terms of E.S.R., joint status and duration, which applied particularly to those patients who were treated with gold.

Coming now to a comparison of the late results and the number of courses of gold treatment and of physical therapy, one finds that the gold-treated patients were better whether they had received one or more courses (see Table 41). For those receiving one course, however, the preponderance seemed greatest. Thus,

Table 40. End results in gold-treated and not gold-treated patients given different number of courses.

End results	Number of courses of treatment					
	1 course		2 courses		3 or more courses	
	Number	Per cent	Number	Per cent	Number	Per cent
Gold-treated patients:						
Symptomless or markedly improved	214	62.0±2.6 [1]	47	45.2±4.9 [1]	19	35.8±6.6
Slightly improved	45	13.0±1.8	15	14.4±3.4	7	13.2±4.6
Relapsed	80	23.2±2.3	31	29.8±4.5	22	41.5±6.8
Unimproved or worse	6	1.7±0.7 [2]	11	10.6±3.0 [2]	5	9.4±4.0
Total	345	100	104	100	53	100
Not gold-treated patients:						
Symptomless or markedly improved	94	47.2±3.5 [3]	29	32.2±4.9 [3]	20	27.4±5.2
Slightly improved	43	21.6±2.9	24	26.7±4.7	17	23.3±4.9
Relapsed	31	15.6±2.6	15	16.7±3.9	21	28.8±5.3
Unimproved or worse	31	15.6±2.6	22	24.4±4.5	15	20.5±4.7
Total	199	100	90	100	73	100

[1] The difference 1 course − 2 courses = 16.8±5.5**.
[2] » » 1 » − 2 » = −8.9±3.1*.
[3] » » 1 » − 2 » = 15.0±6.0*.

Table 41. End results in gold-treated and not gold-treated patients given one or more than one course of treatment.

Number of courses	End results	Gold-treated		Not gold-treated		Differences gold-treated − not gold-treated
		Number	Per cent	Number	Per cent	
1 course	Symptomless or markedly improved	214	62.0±2.6	94	47.2±3.5	14.8±4.4**
	Slightly improved	45	13.0±1.8	43	21.6±2.9	− 8.6±3.4*
	Relapsed	80	23.2±2.3	31	15.6±2.6	7.6±3.5
	Unimproved or worse	6	1.7±0.7	31	15.6±2.6	−13.9±2.7**
	Total	345	100	199	100	—
More than 1 course	Symptomless or markedly improved	66	42.0±3.9	49	30.1±3.6	11.9±5.3
	Slightly improved	22	14.0±2.8	41	25.2±3.4	−11.2±4.4*
	Relapsed	53	33.8±3.8	36	22.1±3.2	11.7±5.0
	Unimproved or worse	16	10.2±2.4	37	22.7±3.3	−12.5±4.1**
	Total	157	100	163	100	—

as appears in Table 41, a larger percentage of those receiving one course of gold treatment were symptomless or markedly improved at follow-up. On the other hand, unimproved or worse patients were relatively more numerous among those given one course of physical therapy. The respective differences are statistically significant. Among patients treated more than once the only significant difference applies to unimproved or aggravated cases which were more frequent in the series not given gold.

As pointed out in the chapter on Materials for Study it proved impractical to concentrate the follow-up study to a short period which instead was extended over the period 1946–50. One reason for this was that many patients failed to answer the first set of questionaries sent out, either because they simply left them unanswered or because they no longer were domiciled at the address given in the available documents and first had to be traced through pensioning authorities or parish registrars. Consequently a varying amount of time elapsed between treatment and follow-up. Here it may be mentioned that at least 3 and at most 11 years passed between the beginning of the first course and the follow-up.

It is of interest to know how the patients' condition changed or fluctuated after treatment for all practical purposes had ceased. Primarily, therefore, the interval between the end of the last course and the follow-up was recorded: and, obviously, this might mean that the end of the last course occasionally was not far removed from the follow-up. The median interval for all gold-treated patients was 5.3 years, for patients given one gold course 5.6 years and for patients given more than one gold course 4.3 years. The median interval for all patients given physiotherapy was 7.1 years, for those receiving one course 7.7 years and for those receiving more than one course 5.7 years. These figures indicate that the interval between the end of the last course of treatment and the follow-up was generally somewhat shorter for those not given gold.

The patients were divided into 4 groups according to the median and quartile of the period elapsed after therapy. The groups represent intervals shorter than 5 years, intervals from 5.0 to 6.9 years, from 7.0 to 7.9 years, and 8 years or longer. (See Table 42.) It will be seen from the table that patients not given gold had somewhat longer intervals regardless of the number of courses. The differences are statistically significant.

In order to establish whether different intervals between the end of the last course and the follow-up had any effect on the late results, the patients were rearranged into three time interval groups. The latter classification conforms with that adopted for Table 42 except for the fact that the last two groups were aggregated, i.e. intervals of 7.0–7.9 years and of 8 years or more were combined into a group of intervals of 7.0 years or longer (Table 43). It appeared that the late results were rather similar after these lengths of time within the gold-treated group and also within the series of patients not given gold. At any rate no signif-

Table 42. Comparison between gold-treated and not gold-treated cases given one or more than one course of treatment with regard to the time interval between the discharge after the last course and the re-examination.

Number of courses	Interval, years	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
		Number	Per cent	Number	Per cent	
1 course	< 5.0	95	27.5 ± 2.4	—	—	27.5 ± 2.4**
	5.0–6.9	166	48.1 ± 2.7	49	24.6 ± 3.1	23.5 ± 4.1**
	7.0–7.9	36	10.4 ± 1.6	71	35.7 ± 3.4	– 25.3 ± 3.8**
	8.0–ω	48	13.9 ± 1.9	79	39.7 ± 3.5	– 25.8 ± 4.0**
	Total	345	100	199	100	—
More than 1 course	< 5.0	113	72.0 ± 3.6	64	39.3 ± 3.8	32.7 ± 5.2**
	5.0–6.9	31	19.7 ± 3.2	57	35.0 ± 3.7	– 15.3 ± 4.9**
	7.0–7.9	10	6.4 ± 2.0	31	19.0 ± 3.1	– 12.6 ± 3.7**
	8.0–ω	3	1.9 ± 1.1	11	6.7 ± 2.0	– 4.8 ± 2.3
	Total	157	100	163	100	—

icant differences were present. The table shows that this applied whether the patients had been given one or more than one course.

Accordingly the different lengths of time which in this study elapsed from the end of the last course of treatment to the follow-up examination apparently had little effect on the late results. It follows that the somewhat longer interval for those given physiotherapy has no effect on the comparison of the late results in gold-treated and not gold-treated patients.

The late results will lastly be considered in the light of the interval between the beginning of the first course of treatment and the follow-up study. This interval will obviously differ little from that shown in Table 43 in those treated once only, but it will of course differ appreciably for those treated several times.

Thus the median interval for those given one gold treatment is 5.8 years and for those treated more than once with gold 6.3 years. The corresponding figures for those not given gold are 7.9 and 8.0 years. A better notion of the distribution will be had from the fact that the upper quartile of the interval from the beginning of the first of more than one course to the follow-up was 8.2 years among the gold-treated patients and 8.7 years among the other patients. Dividing the interval between the beginning of the first course and the follow-up into four groups—6 years or less, 6.0–6.9, 7.0–7.9, and 8 years or more—one finds, just as in the case of the interval from the end of the last course to the follow-up, that those patients not given gold had a longer interval. The respective differences are statistically significant (Table 44).

In Table 45 the late results are divided into two time interval groups, viz. those with intervals under 7 years and those with intervals from 7 years. Being the median common to the gold-treated series and the physiotherapy series, this transition was chosen to make the two series better suited for comparison. How-

Table 43. End results in gold-treated and not gold-treated patients given one or more than one course of treatment, distributed according to the time interval between the discharge after the last course and the re-examination.

Treatment	Number of courses	End results	Interval between the last course and the re-examination, in years: < 5.0 Number	< 5.0 Per cent	5.0–6.9 Number	5.0–6.9 Per cent	7.0 or more Number	7.0 or more Per cent
Gold	1 course	Symptomless	16	16.8±3.8	34	20.5±3.1	13	15.5± 3.9
		Markedly improved	46	48.4±5.1	68	41.0±3.8	37	44.0± 5.4
		Slightly improved	10	10.5±3.1	26	15.7±2.8	9	10.7± 3.4
		Relapsed	22	23.2±4.3	36	21.7±3.2	22	26.2± 4.8
		Unimproved or worse	1	1.1±1.1	2	1.2±0.8	3	3.6± 2.0
		Total	95	100	166	100	84	100
	More than 1 course	Symptomless	9	8.0±2.6	1	3.2±3.2	2	15.4±10.0
		Markedly improved	42	37.2±4.5	10	32.3±8.4	2	15.4±10.0
		Slightly improved	15	13.3±3.2	4	12.9±6.0	3	23.1±11.7
		Relapsed	36	31.9±4.4	12	38.7±8.7	5	38.5±13.5
		Unimproved or worse	11	9.7±2.8	4	12.9±6.0	1	7.7± 7.4
		Total	113	100	31	100	13	100
	Total	Symptomless	25	12.0±2.3	35	17.8±2.7	15	15.5± 3.7
		Markedly improved	88	42.3±3.4	78	39.6±3.5	39	40.2± 5.0
		Slightly improved	25	12.0±2.3	30	15.2±2.6	12	12.4± 3.3
		Relapsed	58	27.9±3.1	48	24.4±3.1	27	27.8± 4.5
		Unimproved or worse	12	5.8±1.6	6	3.0±1.2	4	4.1± 2.0
		Total	208	100	197	100	97	100
Not gold	1 course	Symptomless	—	—	3	6.1±3.4	14	9.3± 2.4
		Markedly improved	—	—	22	44.9±7.1	55	36.7± 3.9
		Slightly improved	—	—	9	18.4±5.5	34	22.7± 3.4
		Relapsed	—	—	10	20.4±5.8	21	14.0± 2.8
		Unimproved or worse	—	—	5	10.2±4.3	26	17.3± 3.1
		Total	—	—	49	100	150	100
	More than 1 course	Symptomless	2	3.1±2.2	3	5.3±3.0	2	4.8± 3.3
		Markedly improved	15	23.4±5.3	16	28.1±6.0	11	26.2± 6.8
		Slightly improved	14	21.9±5.2	16	28.1±6.0	11	26.2± 6.8
		Relapsed	20	31.3±5.8	10	17.5±5.0	6	14.3± 5.4
		Unimproved or worse	13	20.3±5.0	12	21.1±5.4	12	28.6± 7.0
		Total	64	100	57	100	42	100
	Total	Symptomless	2	3.1±2.2	6	5.7±2.3	16	8.3± 2.0
		Markedly improved	15	23.4±5.3	38	35.8±4.7	66	34.4± 3.4
		Slightly improved	14	21.9±5.2	25	23.6±4.1	45	23.4± 3.1
		Relapsed	20	31.3±5.8	20	18.9±3.8	27	14.1± 2.5
		Unimproved or worse	13	20.3±5.0	17	16.0±3.6	38	19.8± 2.9
		Total	64	100	106	100	192	100

Table 44. Comparison between gold-treated and not gold-treated cases with regard to the time interval between the admission to the 1st course of treatment and the re-examination.

Interval, years	Gold-treated		Not gold-treated	
	Number	Per cent	Number	Per cent
< 6.0	251	50.0 ± 2.2 [1]	27	7.5 ± 1.4 [1]
6.0–6.9	108	21.5 ± 1.8	56	15.5 ± 1.9
7.0–7.9	36	7.2 ± 1.2 [2]	106	29.3 ± 2.4 [2]
8.0–ω	107	21.3 ± 1.8 [3]	173	47.8 ± 2.6 [3]
Total	502	100	362	100

[1] Difference gold-treated – not gold-treated = 42.5 ± 2.6**.
[2] » » » – » » » = – 22.1 ± 2.7**.
[3] » » » – » » » = – 26.5 ± 3.2**.

Table 45. End results in gold-treated and not gold-treated patients given one or more than one course of treatment, distributed according to the time interval between the admission to the 1st course and the re-examination.

End results	Gold-treated				Not gold-treated			
	Interval: 1st admission – re-examination				Interval: 1st admission – re-examination			
	< 7.0 years		≧ 7.0 years		< 7.0 years		≧ 7.0 years	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Cases given one course:								
Symptomless or markedly improved	164	63.8 ± 3.0	50	56.8 ± 5.3	24	54.5 ± 7.5	70	45.2 ± 4.0
Slightly improved	36	14.0 ± 2.2	9	10.2 ± 3.2	6	13.6 ± 5.2	37	23.9 ± 3.4
Relapsed	56	21.8 ± 2.6	24	27.3 ± 4.7	9	20.5 ± 6.1	22	14.2 ± 2.8
Unimproved or worse	1	0.4 ± 0.4	5	5.7 ± 2.5	5	11.4 ± 4.8	26	16.8 ± 3.0
Total	257	100	88	100	44	100	155	100
Cases given more than one course:								
Symptomless or markedly improved	46	45.1 ± 4.9	20	36.4 ± 6.5	12	30.8 ± 7.4	37	29.8 ± 4.1
Slightly improved	15	14.7 ± 3.5	7	12.7 ± 4.5	8	20.5 ± 6.5	33	26.6 ± 4.0
Relapsed	30	29.4 ± 4.5	23	41.8 ± 6.7	11	28.2 ± 7.2	25	20.2 ± 3.6
Unimproved or worse	11	10.8 ± 3.1	5	9.1 ± 3.9	8	20.5 ± 6.5	29	23.4 ± 3.8
Total	102	100	55	100	39	100	124	100
All cases:								
Symptomless or markedly improved	210	58.5 ± 2.6	70	49.0 ± 4.2	36	43.4 ± 5.4	107	38.4 ± 2.9
Slightly improved	51	14.2 ± 1.8	16	11.2 ± 2.6	14	16.9 ± 4.1	70	25.1 ± 2.6
Relapsed	86	24.0 ± 2.3	47	32.9 ± 3.9	20	24.1 ± 4.7	47	16.8 ± 2.2
Unimproved or worse	12	3.3 ± 0.9	10	7.0 ± 2.1	13	15.7 ± 4.0	55	19.7 ± 2.4
Total	359	100	143	100	83	100	279	100

ever, not even at these different intervals were there any appreciable differences following gold treatment nor following physiotherapy. (See Table 45.)

The greatest interest, though, belongs to patients treated more than once: the interval for those treated once only deviates little from the previously discussed interval between the end of the last course and the follow-up. But it will be seen that the late results in those treated more than once were similar whether the interval was shorter or longer than 7 years (see Table 45).

It consequently seems as though the unequal lengths of time which elapsed between treatment and follow-up in the present investigation, the differences being rather marked at times, had no particular influence on the late results. It should be noted, however, that the groups so compared were rather small.

CHAPTER 7

AGE AND THERAPY

In preceding chapters we have considered a number of factors capable of affecting the results in a greater or lesser degree, and thereby made it possible to compare on equal terms the data obtained. We saw in the chapter on Materials for Study, however, that both series of patients had approximately the same age distribution. But it is nevertheless interesting to find out if the results of gold therapy and of other treatment are affected in the same way by age.

In the first place, then, the effect of age upon the immediate results of therapy will be investigated. Some patients' exact age when rheumatoid arthritis set in could not be ascertained, so the age at the beginning of the first course of treatment was used as a basis throughout. The patients were divided into three age groups of more or less the same size, namely those less than 30 years old, those aged 30–39 years and those 40 years or more of age, when the first course commenced. The question now arises whether the patients in these groups on the whole had the disease with equal severity. In Table 46 they have therefore been classified as before according to the average number of plus signs per affected joint, i.e. in cases with 1.0–1.1 +, in cases with 1.2–1.4 + and in cases with 1.5 + or more per affected joint.

It appears that the various age groups of gold-treated patients must have comprised cases of about the same severity, for none of the differences are statistically significant. The same applies to those not given gold.

Elsewhere it has been shown that the gold-treated patients had the disease more severely than those not given gold. Comparing now the number of plus signs per affected joint in the various age groups among those given gold and those not given gold, one finds good agreement in the below 30 years age group, whereas the gold-treated cases are more severe in the 30–39 years and in the above 39 years age groups. Thus a higher percentage of patients in the latter groups exhibited 1.5 + or more per joint, while relatively fewer gold-treated patients in the more than 40 years age group had 1.0–1.1 + per joint. The differences are statistically significant.

The results after the first course for the gold-treated patients proved more or less the same in the three age groups, as table 47 shows. This applies to both men and women. For those not given gold, however, the therapeutic effect seemed better in patients younger than 30 years than in persons aged 40 years or more, because the older group included a higher percentage of unimproved or

Table 46. Percentual distribution of gold-treated and not gold-treated cases according to the number of plus per affected joint. The cases are grouped according to the age at the admission to the 1st course of treatment.

Age at the admission	Number of plus per affected joint	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
		Number	Per cent	Number	Per cent	
< 30 years	1.0–1.1	40	30.8 ± 4.0	36	43.4 ± 5.4	– 12.6 ± 6.7
	1.2–1.4	43	33.1 ± 4.1	24	28.9 ± 5.0	4.2
	1.5–ω	47	36.2 ± 4.2	23	27.7 ± 4.9	8.5
	Total	130	100	83	100	—
30–39 years	1.0–1.1	34	25.4 ± 3.8	48	38.4 ± 4.4	– 13.0 ± 5.8
	1.2–1.4	42	31.3 ± 4.0	46	36.8 ± 4.3	– 5.5
	1.5–ω	58	43.3 ± 4.3	31	24.8 ± 3.9	18.5 ± 5.8**
	Total	134	100	125	100	—
≧ 40 years	1.0–1.1	58	24.4 ± 2.8	60	39.0 ± 3.9	– 14.6 ± 4.8**
	1.2–1.4	80	33.6 ± 3.1	53	34.4 ± 3.8	– 0.8
	1.5–ω	100	42.0 ± 3.2	41	26.6 ± 3.6	15.4 ± 4.8**
	Total	238	100	154	100	—

Table 47. Immediate results after the 1st course of treatment in gold-treated and not gold-treated patients, distributed according to the age at the admission.

Age at the admission	Immediate results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
		Number	Per cent	Number	Per cent	
< 30 years	Symptomless	14	10.8 ± 2.7	4	4.8 ± 2.3	6.0 ± 3.5
	Markedly improved	75	57.7 ± 4.3	25	30.1 ± 5.0	27.6 ± 6.6**
	Slightly improved	39	30.0 ± 4.0	44	53.0 ± 5.5	– 23.0 ± 6.8**
	Unimproved or worse	2	1.5 ± 1.1	10	12.0 ± 3.6[1]	– 10.5 ± 3.8*
	Total	130	100	83	100	—
30–39 years	Symptomless	13	9.7 ± 2.6	5	4.0 ± 1.8	5.7 ± 3.2
	Markedly improved	82	61.2 ± 4.2	36	28.8 ± 4.1	32.4 ± 5.9**
	Slightly improved	34	25.4 ± 3.8	67	53.6 ± 4.5	– 28.2 ± 5.9**
	Unimproved or worse	5	3.7 ± 1.6	17	13.6 ± 3.1	– 9.9 ± 3.5*
	Total	134	100	125	100	—
≧ 40 years	Symptomless	12	5.0 ± 1.4	—	—	5.0 ± 1.4**
	Markedly improved	158	66.4 ± 3.1	30	19.5 ± 3.2	46.9 ± 4.5**
	Slightly improved	60	25.2 ± 2.8	86	55.8 ± 4.0	– 30.6 ± 4.9**
	Unimproved or worse	8	3.4 ± 1.2	38	24.7 ± 3.5[1]	– 21.3 ± 3.7**
	Total	238	100	154	100	—

[1] Difference = – 12.7 ± 5.0*.

Table 48. End results in gold-treated and not gold-treated patients, distributed according to the age at the admission to the 1st course of treatment

Age at the admission	End results	Gold-treated		Not gold-treated		Differences gold-treated – not gold-treated
		Number	Per cent	Number	Per cent	
< 30 years	Symptomless	35	26.9 ± 3.9	7	8.4 ± 3.0	18.5 ± 4.9**
	Markedly improved	53	40.8 ± 4.3	40	48.2 ± 5.5	– 7.4
	Slightly improved	14	10.8 ± 2.7	15	18.1 ± 4.2	– 7.3
	Relapsed	26	20.0 ± 3.5	12	14.5 ± 3.9	5.5
	Unimproved or worse	2	1.5 ± 1.1	9	10.8 ± 3.4	– 9.3 ± 3.6*
	Total	130	100	83	100	—
30–39 years	Symptomless	17	12.7 ± 2.9	12	9.6 ± 2.6	3.1
	Markedly improved	66	49.3 ± 4.3	33	26.4 ± 3.9	22.9 ± 5.8**
	Slightly improved	14	10.4 ± 2.6	32	25.6 ± 3.9	– 15.2 ± 4.7**
	Relapsed	28	20.9 ± 3.5	28	22.4 ± 3.7	– 1.5
	Unimproved or worse	9	6.7 ± 2.2	20	16.0 ± 3.3	– 9.3 ± 4.0
	Total	134	100	125	100	—
≧ 40 years	Symptomless	23	9.7 ± 1.9	5	3.2 ± 1.4	6.5 ± 2.4*
	Markedly improved	86	36.1 ± 3.1	46	29.9 ± 3.7	6.2
	Slightly improved	39	16.4 ± 2.4	37	24.0 ± 3.4	– 7.6
	Relapsed	79	33.2 ± 3.1	27	17.5 ± 3.1	15.7 ± 4.4**
	Unimproved or worse	11	4.6 ± 1.4	39	25.3 ± 3.5	– 20.7 ± 3.8**
	Total	238	100	154	100	—
Differences between < 30—30–39 years	Differences between age groups:					
	Symptomless		14.2 ± 4.9*		– 1.2	
	Markedly improved		– 8.5		21.8 ± 6.7**	
	Slightly improved		0.4		– 7.5	
	Relapsed		– 0.9		– 7.9	
	Unimproved or worse		– 5.2 ± 2.5		– 5.2	
Differences between < 30— ≧ 40 years	Symptomless		17.2 ± 4.3**		5.2	
	Markedly improved		4.7		18.3 ± 6.6*	
	Slightly improved		– 5.6		– 5.9	
	Relapsed		– 13.2 ± 4.7*		– 3.0	
	Unimproved or worse		– 3.1 ± 1.8		– 14.5 ± 4.9*	
Differences between 30–39— ≧ 40 years	Symptomless		3.0		6.4 ± 3.0	
	Markedly improved		13.2 ± 5.3		– 3.5	
	Slightly improved		– 6.0		1.6	
	Relapsed		– 12.3 ± 4.7*		4.9	
	Unimproved or worse		2.1		– 9.3 ± 4.8	

aggravated cases. The difference is statistically probable. If men and women are taken separately (a distinction not made in the table), only the men show this difference. For a larger percentage of the men in the younger group (48.5 ± 8.7 per cent) had improved markedly than in the older group (19.1 ± 4.8 per cent),

Table 49. Number of cases aged 15 years at most at the admission to the 1st course of treatment, grouped according to sex, age, number of courses, immediate results after the courses, and end results.

Sex	Age at the admission to the 1st course, in years	Number of courses	Immediate results after the courses	End results
Gold				
M	5	1	symptomless	symptomless
M	8	1	markedly improved	markedly improved
M	10	1	unimproved	slightly improved
F	10	2	after 1st course slightly improved, after 2nd markedly improved	markedly improved
F	10	1	symptomless	symptomless
F	11	1	symptomless	symptomless
F	11	1	unimproved	symptomless
F	14	1	markedly improved	symptomless
F	14	1	symptomless	symptomless
Not gold				
M	9	1	slightly improved	symptomless
M	11	1	slightly improved	markedly improved
M	14	2	after 1st course slightly improved, after 2nd markedly improved	markedly improved
F	8	1	slightly improved	unimproved

the difference (29.4 ± 9.9 per cent) being statistically probable. The women displayed no such differences; and, as shown, the age groups were equivalent with respect to severity of the disease process.

Comparing now, within age groups, the first course of gold therapy and the first course of other therapy, one finds in all age classes a much higher incidence of considerable improvements after gold: a higher percentage of gold cases showed marked improvement, and a higher percentage of non-gold cases were unimproved or became worse. The figures suggest that the high age group included a greater preponderance of markedly improved cases than the younger age groups. A lesser degree of improvement was achieved in a higher proportion of those not given gold. The respective differences are statistically significant or probable. But the age classification of those given gold is not fully comparable with the age classification of the other patients from the aspect of severity. Because, as mentioned, the gold-treated cases were more severe in the middle and the highest age group. This might also imply that at these age levels the effect of gold therapy is more superior to that of other treatment than within the young age group. And the somewhat more favourable immediate results of therapy other than gold in younger than in older patients might be a confirmation of this.

The point to be considered next is the significance of age for the long-term

results. In this respect both gold and other therapy proved more beneficial for young than for old patients: because, judging by the follow-up results, a larger proportion of those given gold became symptomless in the young than in the two older age groups, and there was a higher incidence of marked improvements following other therapy than gold in the young than in the intermediate and old age groups (Table 48). Furthermore, among those not given gold the old age group included a higher percentage of unimproved and aggravated cases than the youngest age group. Again, among those showing initial improvement after gold treatment, those who relapsed were oftener old than young. The respective differences are statistically significant or probable.

If, lastly, the follow-up results following gold treatment and other therapy are considered in relation to age, gold treatment will prove to have been more efficacious in all three age groups. Complete remission of symptoms or marked improvement or both these degrees added were preponderant in all three age groups of gold-treated patients, whereas those not given gold constituted a higher percentage of unimproved and aggravated cases. The differences are statistically significant or probable. Considering that the patients in the intermediate and high age groups had the disease more severely in the gold-treated than in the other patients, the effect of gold can probably be regarded as even more superior in these two age groups compared with the lowest age group.

Gold treatment for rheumatoid arthritis thus proves superior to other therapy in both young and old persons, judging by immediate results as well as by long-term effects. The immediate effects of gold in young and old seem on the whole equivalent, but young are somewhat more benefited than old by physical therapy. With regard to the late prognosis both gold and physical therapy give rise to better results in young than in old patients.

It seems fitting in this chapter to consider also the prognosis for children with rheumatoid arthritis. At most 15 years old when the first course began were 3 boys and 6 girls treated with gold and 3 boys and one girl not given gold. Only one gold-treated girl and one boy not given gold underwent two courses; the remainder received one course. Among the 9 gold-treated children 6 were symptomless and 2 markedly improved at the follow-up examination, whereas then one proved symptomless and 2 markedly improved of the 4 children which were not given gold. Noteworthy discrepancies between the immediate and the late results were found in only one gold-treated and 2 other cases. Immediately after treatment these displayed little or no improvement, but they were symptomless or markedly improved at the follow-up examination. In this investigation, therefore, the prognosis for children with rheumatoid arthritis was comparatively good. But the cases were of course too few to warrant any conclusions or comparisons between gold and other therapy. Table 49 provides a survey of these cases.

GOLD TREATMENT

The dosage of gold drugs among these patients has in part been accounted for by SUNDELIN in 1941 and 1948. In this connection it should be noted that during the period concerned the brand of gold preparation used has obviously changed. Formerly sanocrysin was employed, for example in about 30 per cent of those given one course of treatment. Later aurothion became more prevalent (being used in about 35 per cent of those given one course). The increasing use of aurothion is demonstrated by the fact that more than half the patients (56 per cent) received it in the second course of treatment. Other preparations have been used too, namely aurodetoxin, myoral, neosolganal and solganal B oleosum.[1]

The gold drugs used containing different proportions of elemental gold, and the dosage for various reasons being individualized, a true assessment of the effect necessitated that the amount of gold per injection and course be cal-

Table 50. Median and quartiles of the gold amount (g metallic gold) used for cases given one course of treatment, and of the amount used during the 2nd course of treatment for cases given at least 2 courses.

Course of treatment	Completed or interrupted course of treatment	Number of cases	Metallic gold, g		
			Lower quartile	Median	Upper quartile
1st course	Completed course	255	0.48	0.71	0.94
	Course interrupted because of complications	69	0.18	0.29	0.57
	Course interrupted for no medical reason	21	0.21	0.29	0.43
	All cases given one course	345	0.36	0.61	0.85
2nd course	Completed course	139	0.79	1.03	1.22
	Course interrupted because of complications	13[2]	0.36	0.42	0.56
	Course interrupted for no medical reason	5	0.16	0.19	0.53
	All cases given at least 2 courses	157[3]	0.71	0.99	1.13

[1] Most of these gold preparations have been known since the beginning of gold therapy. Two of them, i.e. aurothion (sodium aurothiosulphate + sodium thiosulphate with 9.8% Au) and myoral (calcium aurothioglycolate with 64% Au) have in recent years been manufactured by the Swedish drug manufacturing company ASTRA.

[2] Of these, 5 cases had complications during the 1st course.

[3] Of these, 21 cases had severe reactions during the 1st course.

Table 51. Preparation amounts (in grammes), metallic gold (in grammes), and mean number of injections per course of treatment, as well as mean amount of metallic gold per injection (in grammes), for cases with completed treatment, cases with treatment interrupted because of complications, and cases with treatment interrupted for no medical reason. 1st course and 2nd course.

Gold preparation	Completed courses					Courses interrupted because of complications					Courses interrupted for no medical reason				
	Number of cases	Preparation amounts per course g	Metallic gold per course g	Number of injections per course	Metallic gold per injection g	Number of cases	Preparation amounts per course g	Metallic gold per course g	Number of injections per course	Metallic gold per injection g	Number of cases	Preparation amounts per course g	Metallic gold per course g	Number of injections per course	Metallic gold per injection g
Cases given only one course:															
Aurothion	84	9.09	0.89	8.7	0.10	31	5.15	0.50	5.5	0.09	5	5.14	0.50	5.4	0.09
Neosolganal	54	3.36	0.47	9.7	0.05	6	1.38	0.19	5.0	0.04	6	1.16	0.16	4.3	0.04
Sanocrysin	70	2.03	0.76	9.5	0.08	26	0.70	0.26	5.0	0.05	7	0.87	0.33	5.7	0.06
Others	47	—	0.78	10.6	0.07	6	—	0.26	3.7	0.07	3	—	0.25	4.0	0.06
Total	255	—	0.75	9.5	0.08	69	—	0.36	5.1	0.07	21	—	0.31	5.0	0.06
The 1st course for cases given several courses:															
Aurothion	28	10.70	1.05	9.4	0.11	9	4.81	0.47	5.8	0.08	—	—	—	—	—
Neosolganal	22	4.57	0.64	11.4	0.06	3	1.71	0.24	6.0	0.04	—	—	—	—	—
Sanocrysin	56	2.02	0.76	10.6	0.07	7	1.12	0.42	6.4	0.07	—	—	—	—	—
Others	30	—	0.80	11.1	0.07	2	—	0.83	9.5	0.09	—	—	—	—	—
Total	136	—	0.81	10.6	0.08	21	—	0.45	6.4	0.07	—	—	—	—	—
The 2nd course for cases given several courses:															
Aurothion	79	11.50	1.13	9.7	0.12	7	5.28	0.52	5.9	0.09	2	2.81	0.28	3.0	0.09
Neosolganal	14	4.75	0.67	10.1	0.07	3	2.16	0.30	6.7	0.05	1	1.05	0.15	5.0	0.03
Sanocrysin	27	2.71	1.01	10.7	0.09	1	0.50	0.19	3.0	0.06	1	0.40	0.15	2.0	0.08
Others	19	—	0.93	10.3	0.09	2	—	0.32	6.0	0.05	1	—	0.29	4.0	0.07
Total	139	—	1.03	10.0	0.10	13	—	0.41	5.8	0.07	5	—	0.23	3.4	0.07

Table 52. Immediate results after the 1st and after the 2nd course of treatment in patients given varying amounts of metallic gold.

	Immediate results after the 1st and after the 2nd course	Amounts of metallic gold per course of treatment (grammes)					
		< 0.60		0.60–0.89		0.90 or more	
		Number	Per cent	Number	Per cent	Number	Per cent
The 1st course in patients given only one course	Symptomless . . .	17	10.1 ± 2.3	13	13.5 ± 3.5	5	6.3 ± 2.7
	Markedly improved	102	60.4 ± 3.8	58	60.4 ± 5.0	50	62.5 ± 5.4
	Slightly improved .	43	25.4 ± 3.3	23	24.0 ± 4.4	24	30.0 ± 5.1
	Unimproved . . .	7	4.1 ± 1.5	2	2.1 ± 1.5	1	1.3 ± 1.3
	Worse	—	—	—	—	—	—
	Total	169	100	96	100	80	100
The 1st course in patients given several courses	Symptomless . . .	1	1.8 ± 1.8	2	4.8 ± 3.3	1	1.7 ± 1.7
	Markedly improved	38	69.1 ± 6.2	28	66.7 ± 7.3	39	65.0 ± 6.2
	Slightly improved .	14	25.5 ± 5.9	11	26.2 ± 6.8	18	30.0 ± 5.9
	Unimproved . . .	2	3.6 ± 2.5	1	2.4 ± 2.4	2	3.3 ± 2.3
	Worse	—	—	—	—	—	—
	Total	55	100	42	100	60	100
The 2nd course in patients given several courses	Symptomless . . .	—	—	—	—	2	2.2 ± 1.5
	Markedly improved	18	66.7 ± 9.1	20	54.1 ± 8.2	58	62.4 ± 5.0
	Slightly improved .	5	18.5 ± 7.5	14	37.8 ± 8.0	23	24.7 ± 4.5
	Unimproved . . .	3	11.1 ± 6.0	3	8.1 ± 4.5	8	8.6 ± 2.9
	Worse	1	3.7 ± 3.7	—	—	2	2.2 ± 1.5
	Total	27	100	37	100	93	100

culated. Here it may be mentioned that the treatment sometimes was discontinued because of severe reactions, sometimes on non-medical grounds.

One-course patients received an average of 8.3 injections with a mean total content of 0.64 g pure gold. Generally the corresponding figures for the second course were higher, the means being 9.5 injections and 0.95 g of gold.

An impression of how the amount of gold given per course varied is provided by Table 50. It gives medians and quartiles partly for patients given one course, partly for the second course for patients treated more than once. It further shows the amounts of gold in courses discontinued on account of severe reactions or for other reasons. It will be seen that reactions leading to cessation of treatment occurred in 20 per cent of the patients given one course only and in 8.3 per cent of those given a second course. It is of interest to note that the number of patients displaying such reactions during both the first and second course was low, viz. 5 persons only.

Another matter to be considered is, for each gold drug used, the mean number of injections and amounts of preparation and gold. Only those gold drugs are specified, however, which were much used, viz. aurothion, neosolganal and

Table 53. End results in patients given varying amounts of metallic gold during the 1st and during the 2nd course of treatment.

	End results	Amounts of metallic gold per course of treatment (grammes)					
		< 0.60		0.60–0.89		0.90 or more	
		Number	Per cent	Number	Per cent	Number	Per cent
The 1st course in patients given only one course	Symptomless . . .	33	19.5±3.0	20	20.8±4.1	10	12.5±3.7
	Markedly improved	72	42.6±3.8	40	41.7±5.0	39	48.8±5.6
	Slightly improved .	23	13.6±2.6	10	10.4±3.1	12	15.0±4.0
	Relapsed	37	21.9±3.2	25	26.0±4.5	18	22.5±4.7
	Unimproved . . .	2	1.2±0.8	1	1.0±1.0	1	1.3±1.3
	Worse	2	1.2±0.8	—	—	—	—
	Total	169	100	96	100	80	100
The 1st course in patients given several courses	Symptomless . . .	8	14.5±4.7	2	4.8±3.3	2	3.3±2.3
	Markedly improved	18	32.7±6.3	13	31.0±7.1	23	38.3±6.3
	Slightly improved .	5	9.1±3.9	8	19.0±6.1	9	15.0±4.6
	Relapsed	19	34.5±6.4	13	31.0±7.1	21	35.0±6.2
	Unimproved . . .	4	7.3±3.5	3	7.1±4.0	3	5.0±2.8
	Worse	1	1.8±1.8	3	7.1±4.0	2	3.3±2.3
	Total	55	100	42	100	60	100
The 2nd course in patients given several courses	Symptomless . . .	2	7.4±5.0	3	8.1±4.5	7	7.5±2.7
	Markedly improved	9	33.3±9.1	14	37.8±8.0	31	33.3±4.9
	Slightly improved .	6	22.2±8.0	3	8.1±4.5	13	14.0±3.6
	Relapsed	7	25.9±8.4	10	27.0±7.3	36	38.7±5.1
	Unimproved . . .	1	3.7±3.7	5	13.5±5.6	4	4.3±2.1
	Worse	2	7.4±5.0	2	5.4±3.7	2	2.2±1.5
	Total	27	100	37	100	93	100

sanocrysin, the remainder being combined in one group. The respective figures will be found in Table 51.

A point of considerable significance is the relationship between different gold doses and the results. To study this the patients were divided into three groups, namely those given less than 0.60 g of metallic gold per course, those given 0.60–0.89 g, and those given at least 0.90 g (Table 52).

The immediate results of treatment with these amounts of gold display no appreciable differences. So, for example it can be computed that while 4.3 per cent of those with high dosages during the first course became symptomless, the same occurred in 10.9 per cent of those with moderate dosages and in 8.0 per cent of those with small dosages, but from statistical points of view these differences are neither significant nor probable.

Nor at follow-up were there any considerable differences among the three dosage groups (Table 53).

As we know it has been stated that the joints show considerable improvement

Table 54. Immediate results after the 1st course of treatment, and end results, in gold-treated patients with or without severe reactions during the 1st course.

Results	With severe reactions		Without severe reactions		Differences
	Number	Per cent	Number	Per cent	
Immediate results after the 1st course:					
Symptomless or markedly improved	73	81.1 ± 4.1	281	68.2 ± 2.3	12.9 ± 4.7*
Slightly improved	15	16.7 ± 3.9	118	28.6 ± 2.2	−11.9 ± 4.5*
Unimproved	2	2.2 ± 1.5	13	3.2 ± 0.9	− 1.0 ± 1.7
Worse	—	—	—	—	—
Total	90	100	412	100	—
End results:					
Symptomless or markedly improved	53	58.9 ± 5.2	227	55.1 ± 2.5	3.8 ± 5.8
Slightly improved	11	12.2 ± 3.4	56	13.6 ± 1.7	− 1.4 ± 3.8
Relapsed	25	27.8 ± 4.7	108	26.2 ± 2.2	1.6 ± 5.2
Unimproved	—	—	14	3.4 ± 0.9	− 3.4 ± 0.9**
Worse	1	1.1 ± 1.1	7	1.7 ± 0.6	− 0.6 ± 1.3
Total	90	100	412	100	—

when reactions, particularly severe reactions, occur in conjunction with gold therapy (cf. Review of the Literature). Table 54 gives the necessary data for those 90 patients in whom severe reactions made it necessary to discontinue the first course of gold treatment[1], and the corresponding data for the remaining gold-treated patients. It appears that symptomless and markedly improved patients were rather more numerous among those exhibiting such reactions, i.e. 81.1 as against 68.2 per cent. Being 12.9 ± 4.7 per cent, the difference is statistically probable. With regard to the long-term results all that can be said is that a higher proportion of those not showing severe reactions were unimproved or aggravated. The difference, 4.0 ± 1.6 per cent, is also statistically probable.

For the third and subsequent gold courses the material is insufficient for statistical analysis, so these courses will be passed over.

It can be said, therefore, that the results obtained suggest that a smaller total amount of gold produces results as good as a larger total amount. It should be noted, though, that the patients given less gold include precisely those whose intolerance made it necessary to discontinue treatment and who seemed to respond slightly better than the others.

[1] In 48 of these cases there was one gold reaction, in the remainder two or more. The most significant complications were: exfoliative dermatitis, 18 cases, drug exanthema, 32 cases, severe pruritus, 8 cases, grave eosinophilia, 12 cases, stomatitis, 13 cases, gustatory disturbances, 4 cases, diarrhoea, 5 cases, granulocytopenia, 10 cases, nephrosis, 3 cases, encephalitis, 3 cases, and bronchopneumonia in 2 cases.

CHAPTER 9

WORKING CAPACITY

The follow-up assessment included an estimate of the patients' working capacity at that time. However, a person's opinion of his own working capacity occasionally fails to conform to that of an unbiassed observer. By mentioning that their replies in no way would jeopardize their pensions or other benefits, we attempted to induce the patients to give correct answers. But it would nevertheless be unwise to expect full parity between residual symptoms and working capacity. For the working capacity depends not only on the patient's symptoms and the disabling power of the disease, but also on psychological factors such as the patient's initiative and willingness to work, etc., not to mention his opportunities for getting work and other social factors. Consider, for example, married women with exclusively domestic duties, who would seem to have a wide scope for adapting their work to their condition.

In the questionary used for the follow-up study the patients were asked to state whether they were wholly or partly able to work and, if so, in what occupation, whether they were completely unfit for work, and whether they suffered from any disease other than rheumatoid arthritis (cf. Fig. 1). According to its demands on physical fitness, work was graded as light, moderate and heavy. Sometimes the boundaries between such classes must of course be rather diffuse. To mention some examples, clerical work was considered light, most industrial occupations were regarded as moderately heavy, and employees in forestry, agriculture, the construction and building trades, etc., were judged to have heavy work.

Data on the working capacity of the gold-treated patients and of the controls at the time of the follow-up study are given in Table 55. The subjects are classified in the three groups just mentioned. The working capacity at follow-up of the gold-treated patients was not appreciably different from that of the controls. Thus, 33.7 per cent of those receiving gold and 35.9 per cent of the controls were fully fit for work. Partially disabled were 55.6 and 54.4 per cent and completely disabled 10.8 and 9.7 per cent respectively. While the majority of those fully fit for work were in light or moderately heavy occupations, most of the partially disabled subjects had light work. On the whole similar proportions of the gold-treated patients and of the controls had light or moderately heavy work. A larger percentage of the comparatively few patients with heavy work had not received gold therapy.

Table 55. Percentual distribution of gold-treated and not gold-treated patients according to the working capacity at the re-examination and the severity of the work.

Working capacity	Severity of work	Gold-treated		Not gold-treated	
		Number	Per cent of all cases	Number	Per cent of all cases
All cases		502		362	
Full	Light	84	16.7 ± 1.7	57	15.7 ± 1.9
	Moderate	75	14.9 ± 1.6	48	13.3 ± 1.8
	Heavy	10	2.0 ± 0.6 [1]	25	6.9 ± 1.3 [1]
	Cases with full working capacity	169	33.7 ± 2.1	130	35.9 ± 2.5
Partial	Light	208	41.4 ± 2.2	136	37.6 ± 2.5
	Moderate	64	12.7 ± 1.5	33	9.1 ± 1.5
	Heavy	7	1.4 ± 0.5 [2]	28	7.7 ± 1.4 [2]
	Cases with partial working capacity	279	55.6 ± 2.2	197	54.4 ± 2.6
No working capacity		54	10.8 ± 1.4	35	9.7 ± 1.6

[1] Difference gold-treated – not gold-treated = $-4.9 \pm 1.4^{**}$
[2] » » » – » » » = $-6.3 \pm 1.5^{**}$.

Not even when the patients were classified by sex was there any appreciable difference in working capacity between gold-treated subjects and the controls (Table 56). Then the preponderance of those undergoing physical therapy among those fit for heavy work was found only among men, partially able to work. In respect of the working capacities of men and women it was found that 44.7 per cent of the gold-treated men and 43.2 per cent of the male controls had unimpaired working capacity, while the corresponding figures for women were 28.9 and 30.8 per cent. There was no manifest difference between the working capacities of married and unmarried women.

Setting the working capacity in relation to the end results, we find that markedly improved female controls and relapsed female controls had somewhat better working capacity than the corresponding groups of gold-treated women. The respective differences are statistically probable (Table 57). However, otherwise neither significant nor probable differences appeared. As one would expect, patients showing marked improvement had better working capacity than those exhibiting slight improvement or aggravation. Remarkably enough not all gold-treated patients who had become symptomless were fully fit for work. Some of these subjects, however, had other diseases that could have impaired their working capacity. The analysis of the relationship between the end results and the capacity for work included an analysis of the grouping with respect to the type of work. Nothing of particular interest came of this analysis, however, perhaps because the subgroups obtained were rather small.

Table 56. Percentual distribution of gold-treated and not gold-treated men and women according to the working capacity at the re-examination and the severity of the work.

Working capacity and severity of work	Gold-treated		Not gold-treated	
	Number	Per cent of total number	Number	Per cent of total number
Total number of men	152		148	
With full working capacity				
Light work	25	16.4±3.0	15	10.1±2.5
Moderate work	33	21.7±3.3	29	19.6±3.3
Heavy work	10	6.6±2.0	20	13.5±2.8
Total	68	44.7±4.0	64	43.2±4.1
With partial working capacity				
Light work	29	19.1±3.2	24	16.2±3.0
Moderate work	36	23.7±3.4	23	15.5±3.0
Heavy work	6	3.9±1.6 [1]	24	16.2±3.0 [1]
Total	71	46.7±4.0	71	48.0±4.1
With no working capacity	13	8.6±2.3	13	8.8±2.3
Total number of women	350		214	
With full working capacity				
Light work	59	16.9±2.0	42	19.6±2.7
Moderate work	42	12.0±1.7	19	8.9±1.9
Heavy work	—	—	5	2.3±1.0
Total	101	28.9±2.4	66	30.8±3.2
With partial working capacity				
Light work	179	51.1±2.7	112	52.3±3.3
Moderate work	28	8.0±1.5	10	4.7±1.4
Heavy work	1	0.3±0.3	4	1.9±0.9
Total	208	59.4±2.6	126	58.9±3.4
With no working capacity	41	11.7±1.7	22	10.3±21

[1] Difference gold-treated – not gold-treated = $-12.3 \pm 3.4^{**}$.

Working capacity is also influenced by age. However, as a special investigation showed that the gold-treated patients' age distribution at the time of the follow-up study resembled that of the controls, the two series may be considered equivalent in this respect.

Those with disabling diseases other than rheumatoid arthritis were next excluded from the series, but even then the gold-treated patients and the controls had practically the same working capacity.

Table 57. Percentual distribution according to the working capacity of gold-treated and not gold-treated men and women with different end results.

Sex	End results	Working capacity	Gold-treated			Not gold-treated		
			Total	Number	Per cent of total	Total	Number	Per cent of total
Men	Symptomless	Full		25	86.2±6.4		11	100.0
		Partial	29	4	13.8±6.4	11	—	—
		None		—	—		—	—
	Markedly improved	Full		39	58.2±6.0		37	66.1±6.3
		Partial	67	27	40.3±6.0	56	18	32.1±6.2
		None		1	1.5±1.5		1	1.8±1.8
	Slightly improved	Full		3	11.1±6.0		9	28.1±7.9
		Partial	27	21	77.8±8.0	32	23	71.9±7.9
		None		3	11.1±6.0		—	—
	Relapsed	Full		1	4.2±4.1		7	26.9±8.7
		Partial	24	18	75.0±8.8	26	18	69.2±9.1
		None		5	20.8±8.3		1	3.8±3.7
	Unimproved or worse	Full		—	—		—	—
		Partial	5	1	20.0	23	12	52.2±10.4
		None		4	80.0		11	47.8±10.4
Women	Symptomless	Full		42	91.3±4.2		13	100.0
		Partial	46	4	8.7±4.2	13	—	—
		None		—	—		—	—
	Markedly improved	Full		46	33.3±4.0 [1]		33	52.4±6.3 [1]
		Partial	138	90	65.2±4.1	63	30	47.6±6.3
		None		2	1.4±1.0		—	—
	Slightly improved	Full		6	15.0±5.6		8	15.4±5.0
		Partial	40	31	77.5±6.6	52	41	78.8±5.7
		None		3	7.5±4.2		3	5.8±3.2
	Relapsed	Full		3	2.8±1.6 [2]		8	19.5±6.2 [2]
		Partial	109	75	68.8±4.4	41	27	65.9±7.4
		None		31	28.4±4.3		6	14.6±5.5
	Unimproved or worse	Full		4	23.5±10.3		4	8.9±4.2
		Partial	17	8	47.1±12.1	45	28	62.2±7.2
		None		5	29.4±11.0		13	28.9±6.8

[1] Difference gold-treated – not gold-treated = – 19.1±7.5*.

[2] » » » – » » » = – 16.7±6.4*.

Consequently, apart from a somewhat better working capacity in a few small groups of the controls, the working capacities of these two categories were practically the same at the time of the follow-up study. In coming to this conclusion it was obviously impossible to take into account every factor of potential significance. In view of the gold-treated patients' more favourable end results, one would also expect their working capacity to be better. Probably this must be

Table 58. Gold-treated and not gold-treated patients who had a pension at the re-examination or to whom a pension was granted within one year afterwards, in per cent of the cases with partial or no working capacity.

Working capacity	Sex	Gold-treated			Not gold-treated			Differences gold-treated – not gold-treated
		Total number	Number of cases with pension		Total number	Number of cases with pension		
			Number	Per cent of total number		Number	Per cent of total number	
Partial	Men	71	19	26.8±5.3	71	18	25.4±5.2	1.4
	Women . .	208	46	22.1±2.9	126	28	22.2±3.7	−0.1
	Both sexes .	279	65	23.3±2.5	197	46	23.4±3.0	−0.1
None	Men	13	9	69.2	13	9	69.2	0
	Women . .	41	28	68.3±7.3	22	15	68.2±0.1	0.1
	Both sexes .	54	37	68.5±6.3	35	24	68.6±7.8	−0.1
Total	Men	84	28	33.3±5.1	84	27	32.1±5.1	1.2
	Women . .	249	74	29.7±2.9	148	43	29.1±3.7	0.6
	Both sexes .	333	102	30.6±2.5	232	70	30.2±3.0	0.4

attributed to the fact that the gold-treated patients on the whole had more severe forms of rheumatoid arthritis than the controls, as appears from the detailed analysis given elsewhere.

In an attempt to clear up this point the Board of Pensions was asked to furnish the names of those patients, partially or wholly unable to work, who were receiving or had applied for disability pensions. Those who at the time of the follow-up investigation were or within a year thereafter had become pensioned are listed in Table 58. It should be noted, however, that no information was secured regarding 32 of those receiving gold and 12 of the controls. The table reveals that no appreciable differences existed between those receiving gold and the controls nor between men and women. Probably those who were pensioned within a year of the follow-up study had a markedly reduced working capacity at that time already. But even after these patients have been excluded and only those are considered who actually were pensioned when followed up, no appreciable difference emerges between the gold-treated patients and the controls (26.4 and 27.2 per cent respectively).

Next we investigated how many at the time of the follow-up study received or within a year thereof were granted pensions among those who then were wholly or partly unable to work despite showing improvement. Here we are thus concerned with those classified as symptomless or markedly improved who were wholly or partly unable to work and with those considered slightly improved although unable to work. (These patients have been dealt with before in Table 57.) This brought to light a difference between the gold-treated patients and the

Table 59. Gold-treated and not gold-treated patients who had a pension at the re-examination or to whom a pension was granted within one year afterwards, in per cent of the cases with partial or no working capacity whose state of health did not agree with their working capacity (see Table 57).

Sex	Gold-treated			Not gold-treated			Differences gold-treated – not gold-treated
	Total number	Number of cases with pension		Total number	Number of cases with pension		
		No.	Per cent of total number		No.	Per cent of total number	
Men	35	6	17.1±6.3	19	0	0	17.1±6.3*
Women	99	18	18.2±3.9	33	1	3.0±3.0	15.2±4.9**
Both sexes . .	134	24	17.9±3.3	52	1	1.9±1.9	16.0±3.8**

controls which was significant for women and probable for men. These results appear in Table 59. Remarkably enough, as mentioned, not all the gold-treated subjects who became symptomless (4 men and 4 women) were fully fit for work. Pensions had been granted to two of them, but these had other diseases too. Yet, even if the 8 symptomless patients are excluded, the difference between gold-treated patients and controls who were receiving pensions remained significant (15.6 ± 3.9 per cent). And if those who were granted pensions within a year of the follow-up study also are eliminated, the difference still is significant (13.2 ± 3.7 per cent). The fact that those gold-treated patients who showed improvement but had reduced working capacity were granted pensions more frequently than the corresponding controls evidently suggests that these gold-treated cases proved more severe when followed up than the controls did. This to some extent explains why the gold-treated patients, despite showing better end results than the controls, did not also have a better working capacity.

The fact that the gold-treated cases initially were more severe than those receiving physical therapy has previously been emphasized. As we have seen, a larger proportion of those receiving gold treatment exhibited high E.S.R. readings, had slightly more severe joint disturbances in terms of average number of plus signs per affected joint, and displayed longer histories. For the groups with different grades of working capacity mean values have here been computed with respect to the initial E.S.R., the joint status in terms of plus per affected joint and the length of history at the beginning of therapy (Table 60). A difference in initial E.S.R. and joint condition was then found between the gold-treated patients and the controls, particularly among those who were partly or wholly unable to work. The mean E.S.R. value, for example, was much higher for those gold-treated men with impaired working capacity who showed improvement immediately after therapy and then became worse than for the corresponding controls. The mean E.S.R. value was higher for all the gold-treated women with reduced or no working capacity than for the corresponding controls. (These two differences are statistically significant.) These same groups of women also

Table 60. **Means, standard errors of the means and standard deviations of E.S.R. (mm) and number of pairs [illegible] the beginning of the 1st course of treatment in gold-treated and not gold-treated patients, grouped according to agreement of working capacity with end results.** (The groups are taken from table 57. With regard to the groups with different end results, see below.)

At the beginning of 1st course of treatment	Sex	End results	Gold-treated No.	Gold-treated $M \pm \varepsilon(M)$	Gold-treated σ	Not gold-treated No.	Not gold-treated $M \pm \varepsilon(M)$	Not gold-treated σ	Differences gold-treated – not gold-treated
E.S.R.	Men	1. Full working capacity	68	23.0 ± 2.0	16.2	64	22.5 ± 2.5	20.1	0.5
		2. Partial or no working capacity	84	33.5 ± 2.6	23.5	84	24.5 ± 2.6	23.8	9.0 ± 3.7
		In cases No. 2 the state of health:							
		a. does not agree with working capacity	35	29.9 ± 3.8	22.3	19	23.3 ± 5.1	22.3	6.6
		b. is doubtful	23	31.2 ± 4.1	19.8	19	14.6 ± 2.7	11.7	16.6 ± 4.9**
		c. agrees with working capacity	26	40.5 ± 5.4	27.6	46	29.1 ± 4.0	27.1	11.4 ± 6.7
	Women	1. Full working capacity	101	28.7 ± 1.8	17.8	66	28.5 ± 2.2	17.8	0.2
		2. Partial or no working capacity	249	38.0 ± 1.5	24.0	148	30.5 ± 1.7	20.5	7.5 ± 2.3**
		In cases No. 2 the state of health:							
		a. does not agree with working capacity	99	35.5 ± 2.3	23.1	33	29.2 ± 3.9	22.2	6.3 ± 4.5
		b. is doubtful	106	40.6 ± 2.2	23.1	33	35.4 ± 4.2	24.2	5.2
		c. agrees with working capacity	44	37.2 ± 4.2	27.8	82	29.0 ± 2.0	18.0	8.2 ± 4.7
State of the joints	Men	1. Full working capacity	68	1.309 ± 0.043	0.352	64	1.320 ± 0.038	0.302	– 0.011
		2. Partial or no working capacity	84	1.335 ± 0.031	0.282	84	1.336 ± 0.026	0.239	– 0.001
		In cases No. 2 the state of health:							
		a. does not agree with working capacity	35	1.363 ± 0.056	0.329	19	1.300 ± 0.057	0.247	0.063
		b. is doubtful	23	1.243 ± 0.047	0.225	19	1.353 ± 0.062	0.270	– 0.110
		c. agrees with working capacity	26	1.377 ± 0.050	0.255	46	1.343 ± 0.034	0.229	0.034
	Women	1. Full working capacity	101	1.363 ± 0.035	0.356	66	1.217 ± 0.037	0.298	0.146 ± 0.051*
		2. Partial or no working capacity	249	1.462 ± 0.021	0.338	148	1.284 ± 0.024	0.298	0.178 ± 0.032**
		In cases No. 2 the state of health:							
		a. does not agree with working capacity	99	1.412 ± 0.033	0.329	33	1.191 ± 0.044	0.254	0.221 ± 0.055**
		b. is doubtful	106	1.486 ± 0.033	0.341	33	1.355 ± 0.056	0.319	0.131 ± 0.065
		c. agrees with working capacity	44	1.516 ± 0.051	0.338	82	1.293 ± 0.033	0.299	0.223 ± 0.061**

1. All these cases have full working capacity, irrespective of the state of health.
2. All these cases have partial or no working capacity, irrespective of the state of health.
   a. Symptomless or markedly improved with partial working capacity; symptomless, markedly improved or slightly improved with no

exhibited a significant difference in joint status, but the corresponding men, who were very few, displayed no such difference. Apparently there were no appreciable differences with regard to length of history (not included in the table), but that was expected in view of what has been said before.

In any case there can be no doubt that those gold-treated patients who were wholly or partly unable to work initially had rheumatoid arthritis in a more severe form than the corresponding controls.

APPENDIX

REVIEW OF THE LITERATURE ON HORMONES ALONE AND COMBINED WITH OTHER REMEDIES

In the past two decades gold therapy has advanced to a prominent position among the various procedures used in the control of rheumatoid arthritis. Many authors have evaluated the results of gold therapy very positively, whereas others have felt that the excellent immediate results are impermanent. This appears equally from the literature reviewed elsewhere in this paper and from my own findings. Furthermore gold administration is often attended by severe reactions. As mentioned, such reactions often seem to be associated with beneficial effects on the joint disorder as such, but occasionally they are so grave that many hold them to be great drawbacks which make gold therapy less attractive. Accordingly gold therapy, despite its advantages, has not been considered an ideal method: and, as the review of the literature makes clear, new ways of combating the disease have continually been sought. Perhaps more attention and greater hopes than ever before were aroused by the experiences of cortisone and ACTH in the treatment of rheumatoid arthritis which HENCH *et al.* published in 1949. Subsequently trials with these substances were made on the widest scale in most countries, and a very profuse literature now exists in the field. Most authors have reported that these hormones as a rule have a very beneficial action initially.

Here it should be mentioned that other steroids have of course also been tried in the treatment of rheumatoid arthritis. Most investigators have discovered, however, that apart from cortisone practically the only one with antirheumatic properties is hydrocortisone. (Cf. POLLEY & MASON, 1950; HENCH, 1950; HENCH *et al.*, 1950; BOLAND & HEADLEY, 1952; BOLAND, 1952; CLARK *et al.*, 1952.) Cortisone was originally given by the intramuscular route, but it was soon found that approximately the same results were produced by oral medication in suitable dosage (FREYBERG *et al.*, 1950; WARD *et al.*, 1951; RAGAN *et al.*, 1952; etc.).

But it quickly became apparent to all those who used these drugs in rheumatoid arthritis that the effects, often marvellous at first, as a rule wore off as soon as medication was discontinued, whereupon rapid aggravation set in till the patient's condition was about the same as before treatment. That this would happen was predicted by HENCH *et al.* as early as 1949 after they had used com-

pound E in 16 and ACTH in 4 cases of rheumatoid arthritis. In 1950 the same authors reported the results of treatment with cortisone and/or ACTH in 23 cases of rheumatoid arthritis. After courses ranging from 8 to 187 days 22 of the patients showed very marked improvement. The authors repeated, however, that signs of rheumatic activity usually returned when treatment was discontinued. But the recurrence was in a few cases delayed for some weeks or months and in one case the remission had even lasted for a year. Jonsson *et al.* (1949), who in 1949 already began to give ACTH for rheumatoid arthritis, found that the E.S.R. values tended to rise as the dosage was diminished. In 1950 Jonsson stated that the effect sets in rapidly and goes just as rapidly. Furthermore, Boland & Headly (1949), having rapidly obtained remarkable results with cortisone in various cases including 5 severe and active ones, observed that the arthritic symptoms recurred in all patients after withdrawal of cortisone. Having treated 17 cases with cortisone and 16 with ACTH for periods up to 160 days, Freyberg (1950) reported that relapse occurs at varying periods of time after cessation of therapy. Crain *et al.* (1950) treated 14 cases with cortisone or ACTH with results resembling those reported by others: within 2 to 30 days after the end of therapy they usually noted a reversion to the pretreatment state. Engleman (1950) who in 18 cases had administered cortisone for periods ranging from 12 to 58 days obtained relapses to the state before treatment in all cases when administration was discontinued. Stone *et al.* (1950) intermittently over a 12-month period gave cortisone and ACTH to 7 patients. The symptoms returned when the hormones were withdrawn, the longest period of improvement among their patients being 4½ months. Bayles *et al.* (1951) emphasized that relapse occurred within 10 days after the end of treatment in 90 per cent of 135 cases. Treating 50 cases with cortisone, Bilka (1951) obtained marked relief in 65 per cent and moderate in 15 per cent; after the end of therapy immediate loss of improvement occurred in 50 per cent and slower loss of improvement in 45 per cent of the cases. After treating a series of cases continuously for 12 months or longer, Freyberg *et al.* (1951) maintained that early and severe relapses were the rule after withdrawal of cortisone, even after prolonged administration and in cases with short histories. Rosenberg (1952) noted that discontinuation of hormone administration consistently leads to prompt recurrence of symptoms.

Various kinds of side-effects have generally made it impossible continually to administer the large dosages required for therapeutic effects. In order to prolong the action of these hormones varying dosage schedules have therefore been tried. Having produced improvement by means of comparatively high initial doses, most investigators have sought to prolong the improvement with smaller maintenance doses. Others, but these are few, have aimed at the same result by giving very large doses over a short period. Bayles *et al.* (1951), for example, gave large cortisone doses (500 mg) daily for 2 to 4 weeks in 12 cases. Promising results were recorded in 5 cases which were followed up for 74 to 88 days and in 4 others which were followed up for 13 to 32 days. Chase & Light-

BODY (1952), on the other hand, saw no advantage over the long-term method in short-term, massive-dose cortisone treatment, after trying the latter in 7 severe cases. Some have given endocrine substances intermittently. Thus STONE *et al.* (1950) expressed the opinion that administration should not be continual but repeated at each relapse.

Researchers giving prolonged cortisone or ACTH treatment have usually started with comparatively large doses and continued with gradually diminishing maintenance doses. Some workers, however, have administered increasing doses in the initial phases. Thus COPEMAN *et al.* (1952) stated that favourable results were obtained by giving 100 mg of cortisone daily till improvement commenced and then doubling the dose for a week or two in order to enhance the effect, whereupon they decreased the dosage.

In the treatment of rheumatoid arthritis many authors have used prolonged administration of hormones, generally as fairly small maintenance doses, some of these workers having reported the results obtained (cf. HENCH *et al.*, 1950; BOLAND & HEADLY, 1950; GOSLINGS *et al.*, 1950; WARD *et al.*, 1951; COPEMAN, 1951; BOLAND, 1951; BOLAND & HEADLY, 1951; BILKA, 1951; FREYBERG *et al.*, 1951; PRICE *et al.*, 1952; COPEMAN, 1952; COPEMAN *et al.*, 1952; RAGAN *et al.*, 1951; FISCHER, 1952; BAUER *et al.*, 1952; NORCROSS, 1952; KAMMERER & CECIL, 1953; FISCHER & BROCHNER-MORTENSEN, 1953; WARD *et al.*, 1953). As an example of these authors we may take BOLAND & HEADLY (1950) who treated 36 cases for an average period of 94 days and obtained stable improvement in 35 per cent of severe cases and 100 per cent of mild cases. WARD *et al.* (1951) described a series of 100 cases, stating that good antirheumatic effects often were observed without concomitant side-effects when small doses of cortisone were given by the oral route for several months.

Giving cortisone to 76 patients with rheumatoid arthritis, BOLAND (1951) treated 60 of them uninterruptedly for 6 to 15 months. In about two-thirds of the 76 cases "rheumatic control" could be maintained. FREYBERG *et al.* (1951) treated some patients continually for 12 months or longer. Describing a series of 65 cortisone-treated and 12 ACTH-treated cases, PRICE *et al.* (1952) reported that of the former 45 were treated continuously for two years and 20 for one year or less, and all of the latter had been receiving ACTH for a year or less. Good results were obtained in 74 and 77 per cent and fair results in 22 and 15 per cent of the cases respectively. Seventeen of 20 patients treated for 2 years by COPEMAN (1952) were at work while taking maintenance doses. RAGAN *et al.* (1952) stated that 59 patients who had been treated for 10 to 12 months on an average were less disabled than they were before treatment.

Accordingly, although protracted hormone therapy not seldom seemed to have beneficial effects, it was soon brought home to most workers that such treatment was neither suitable nor indicated in all rheumatoid cases but should be used in selected cases only. This attitude has been taken particularly by those workers who most recently have published their experiences of hormones

in the treatment of rheumatoid arthritis. Fischer (1952). for example, obtained notable improvement or remission in 23 of 34 cases, but most of them were worse when followed up 4 to 12 months later. He concluded that continuous treatment should be reserved for selected cases. Having treated 48 patients with ACTH and or cortisone for periods of 8 to 680 days. Bauer *et al.* (1952) concluded that these agents cannot be widely applied and should never be solely relied upon in the management of the disease. Norcross (1952). commenting on 20 cases treated with ACTH for periods over a year of which 14 had improved and still were receiving ACTH therapy. observed that the seriously ill juvenile rheumatoid patients and the few chronically disabled adults who can afford and tolerate it for a prolonged period will be helped to a considerable degree by ACTH. Kammerer & Cecil (1953) had treated 90 private patients suffering from rheumatoid arthritis with cortisone for periods ranging from 3 weeks to 30 months. The agent had been "a definite and continuing boon" in 34 of these cases. On the basis of their experiences the authors sought to define what forms of rheumatoid arthritis would be most likely to respond to hormone treatment. Having given hormone treatment to 50 patients with rheumatoid arthritis for 2 to 33 months and obtained a good response during therapy in 23 patients. Fischer & Brochner-Mortensen (1953) considered the treatment of practical value in selected cases of rheumatoid arthritis. After registering great or moderate relief in 44 of 46 cases where cortisone had been given continuously for 8 to 24 months. Ward *et al.* (1953) maintained that "cortisone in relatively small doses can be used effectively and safely for prolonged periods in properly selected and carefully managed patients". In addition they stressed that conservative procedures. i.e. physical therapy. etc.. generally should be tried in the first place. Surveying various modes of treatment in rheumatoid arthritis. Jonsson (1953) stated that ACTH and. particularly. cortisone "may have good results in certain forms of rheumatoid arthritis. although indications are not yet fully established". In another surveying article Luft (1953) pointed out that beneficial effects of cortisone should be expected in at most 50 per cent of rheumatoid arthritis cases and that the selection of these cases was a matter of experience. He went on to reaffirm that hormone treatment is effective only so long as any of the hormone administered remains in the organism. and ACTH and cortisone were no exceptions from this principle. Hench (1953). finally. asserted: "The basic requirements for satisfactory results from prolonged hormonal usage are careful selection of cases and individualized treatment."

While attempts were made to achieve more permanent relief from rheumatoid arthritis by varying the dosage of cortisone and ACTH. experiments were under way with combinations of these hormones and other drugs credited with antirheumatic properties. A variety of speculations have been the basis for these combination treatments. Thus hormones have been thought to react synergistically with a number of other drugs. certain agents (e.g. *p*-aminobenzoic acid)

have been said to prevent inactivation of cortisone in the system, or it has been proposed that the rapid action of hormones could be prolonged with the aid of more slowly acting substances such as gold, and so on. It has also been hoped that the disease would respond to smaller doses of the various drugs when these were given combined than when they were given alone, which would tend to reduce the incidence of side effects due to cortisone or to other drugs given in combination therewith, for example gold.

For example HENDERSON *et al.* (1950, 1951), acting on the assumption that there would be synergism between cortisone and insulin, treated 12 cases of rheumatoid arthritis with relatively small doses of cortisone combined with insulin. They obtained major improvement or complete remission in 11 cases. The duration of treatment for maximal benefit varied between 10 and 30 days. The authors claimed they obtained favourable effects with much smaller cortisone doses when they used this combination therapy than otherwise was required for the palliation of rheumatoid arthritis.

Others have combined hormone therapy with salicylates, vitamin C, PABA, butazolidin and similar substances. On the subject of salicylates and vitamin C used in association with hormone therapy, HENCH *et al.* (1950) remarked that their experiments with such a regimen had been disappointing. In 1950 WIESEL *et al.* described 3 cases of rheumatoid arthritis and in 1951 15 cases where cortisone had been given in conjunction with PABA (*p*-aminobenzoic acid). The drugs were given in various proportions and the immediate results were favourable. However, most of the cases relapsed when administration was discontinued. The authors stated that the small doses of cortisone and of PABA used would have been ineffective alone. They supposed that PABA tended to prevent inactivation of cortisone, a theory that was criticized in an annotation in "The Lancet" (261:674:1951). OKA (1953) achieved promising results in 16 of 20 cases of rheumatoid arthritis which he had treated with cortisone and PABA, but mild recurrences took place when therapy was stopped. He found further that the adjunctive use of PABA in cortisone treatment permitted lower cortisone dosage, prevented untoward reactions and reduced cost of treatment.

Phenylbutazone (butazolidin, etc.) has in recent years received widespread use in the treatment of rheumatoid arthritis. Its therapeutic value has been discussed and in many quarters questioned. Its use has been tried in conjunction with cortisone (HOGARDT, 1952; SHULMAN, 1952; etc.). HOGARDT, for example, said that the greatest value of butazolidine used in combination with cortisone therapy was that it made possible a reduction of the cortisone dosage.

At an early stage a number of authors expressed the hope that a combination of cortisone and gold would prove valuable in the control of rheumatoid arthritis. COHEN & MCBRIDE (1950), for example, suggested that a treatment schedule where cortisone initially was followed by ACTH and pregnenolone which in turn was followed by a course of gold therapy might turn out to be an effective regimen. After treating 5 cases of rheumatoid arthritis with small doses

of ACTH for periods of 2 to 6 months, Goslings *et al.* (1950) sought to maintain the improved condition in 4 cases with gold. However, in summing up they wrote: "More experience with this combined form of treatment is required before conclusions can be drawn." Margolis & Caplan (1951) found combined ACTH-gold treatment in rheumatoid arthritis superior to ACTH therapy alone. Using ACTH alone they recorded remission or major improvement in 61 per cent of 33 cases. In most of these cases the effect persisted only as long as treatment was in progress. In 13 cases where gold had not been used previously and in 10 cases which had responded unfavourably to gold they used a combination of ACTH and gold, obtaining remission or major improvement in 77 and 80 per cent of the cases respectively, i.e. higher percentages than when they used ACTH alone. Moreover, the remission or major improvement immediately after ACTH-gold therapy which occurred in 18 cases persisted in 7 cases for 30 to 229 days after withdrawal of the hormone.

Bilka (1951) treated 12 cases with cortisone and gold combined, obtaining approximately the same results as with gold alone. He found no potentiation or inhibition between the actions of these agents but nevertheless found certain advantages in such combination therapy, for it facilitated the control of the active disease during the initial months while adequate gold effect at the same time was being built up. Thompson & Rowe (1952) obtained complete remission in 38.5 per cent of 13 cases when cortisone and gold were given concurrently, in nil per cent of 8 cases when gold therapy was followed by cortisone, in 40.5 per cent of 42 cases when gold was used alone, in 20.7 per cent of 29 cases when cortisone was used alone, and in 4.4 per cent of 273 cases when agents other than cortisone or gold were employed. Significant remission was still present in 3 of the cases treated with cortisone and gold concurrently when they were followed up respectively 88, 163 and 229 days after withdrawal of cortisone. In the authors' opinion simultaneous administration of cortisone and gold arrested rheumatoid arthritis in approximately the same percentage of cases as gold alone, but the combined therapy was superior to cortisone alone. The combination reduced the risks of untoward reactions to gold; it enabled rehabilitative measures to be instituted sooner, i.e. before the gold level had become effective.

Other workers have been unable to see any benefits in combined gold-cortisone treatment. After initially obtaining notable improvement or remission in 23 of 34 severe cases with cortisone alone, Fischer (1952) tried gold as an adjunct in 11 cases without finding any synergism. Egelius *et al.* (1952), who reported a series of 210 gold-treated cases, remarked that they had not been encouraged by combinations of gold and hormone therapy. In 1952 Ralston reviewed the results of combination therapy with gold-cortisone, finding that assessments had been reduced from "hopeful" to "possibly harmful". Analyzing a group of about 85 cases which had been treated by 7 different authors sometimes with gold and cortisone concurrently, sometimes with either substance alone for a varying period before the other was added, he found that the hormonal effect had been

prolonged in 18 of these cases (20 per cent), and that the prolongation could be ascribed to the associated gold therapy.

Clashing opinions about this combined therapy were voiced at the American Rheumatism Association's annual meeting for 1952. Reporting a series of 19 patients with rheumatoid arthritis who had been given various combinations of gold, cortisone and hydrocortisone, ENSIGN & SIGLER deemed combination therapy a more useful approach, particularly in refractory cases. ROSENBAUM, who had employed combination therapy in 40 cases, stated that the gains made with cortisone could be maintained in about half the cases by using gold salts only. He had also found that gold reactions would not occur as long as cortisone was given concurrently with gold. Among others THOMPSON had 15 patients who had shown some improvement on gold alone, but there was no remission when they were given cortisone in addition. On the other hand remission occurred in 9 of 29 cases (31 per cent) where gold and cortisone had been given concurrently. Subsequently the latter patients had been on gold and off cortisone for one year to 18 months. The speaker maintained that the combination of cortisone and gold simultaneously possessed certain advantages. Cortisone together with gold enabled rehabilitative measures to be established before the gold level became effective, and it could be withdrawn when the gold was doing its work. Moreover, the combination seemed to reduce the risk for gold reactions. TRAEGER had treated 18 cases with cortisone and gold simultaneously or with cortisone started before gold or vice versa. He saw no advantages in these combinations other than that cessation of cortisone and subsequent treatment with gold in four cases out of five resulted in control of the arthritic process. KAMMERER reported that with few exceptions he had gained nothing by giving cortisone and gold simultaneously.

COSTE *et al.* (1953) treated a series of 90 patients and another of 50 patients with different combinations of gold and hormones. They found no merits in gold therapy after prolonged hormone treatment; relapses following hormone treatment were not prevented thereby. On the other hand they did attribute certain benefits to concurrent administration of the two agents. It enabled therapeutic gold doses to be quickly introduced into the organism. The following of the authors' therapeutic results may be mentioned. Among 60 patients in the former series they achieved 25 remissions of at least a month and the remainder relapsed. In the other series of 50 cases remissions occurred in 14, relapses in 24, while the results in the other 12 cases were equivocal or doubtful. The authors also reported in the same paper some experiments with gold treatment combined with intra-articular hydrocortisone, apparently favourable results being obtained.

From the foregoing it is evident that opinions are divided about treatment with various combinations of gold and cortisone or ACTH in rheumatoid arthritis. However, some authors have stated that they do find certain therapeutic advantages in such combination therapy.

HORMONES COMBINED WITH GOLD IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Therapeutic trials with various combinations of hormones and gold drugs in the control of rheumatoid arthritis were made in 42 patients during the period from October 1950 to July 1953 at the Pensions Board's Hospital, Nynäshamn. A chronological list, reckoned from the beginning of treatment, of the patients will be found in Table 61. It gives sex, age and years of rheumatoid arthritis at the commencement of therapy, joint status (number of plus signs per person and per affected joint) and E.S.R. (1st hour) at the beginning of treatment and at its end, immediate results of treatment, years elapsed from end of treatment to follow-up examination, joint status and E.S.R. on the latter occasion when estimated, state of health and fitness for work when followed up, and specifications of hormone and gold therapy. The type (brand) and total amount of hormone administered are indicated, both cortisone and Cortone being designated "C". The subscripts *a*, *b*, and *c* after the names of the endocrine preparations denote, respectively, that hormone treatment preceded, parallelled or followed gold therapy. Whenever the two modes of treatment partly overlapped obvious combinations of subscripts are used, for example $a(-b)$ if hormones were given before and during the first few weeks of gold treatment. Finally the table includes data on the gold preparations used, the total number of grammes administered and, parenthetically, the number of injections.

In evaluating the results of this duplex therapy the first thing that comes to mind is to compare them with the results of gold treatment alone, namely the group of 502 gold-treated patients discussed previously, and with the controls for the latter group, i.e. those 362 patients receiving solely physical therapy. However, it must first be determined whether the group of 42 patients undergoing combined therapy can be justifiable compared with the other two groups.

It will be seen that the small group included a substantially larger percentage of women than the gold-treated subjects or the control group. Thus 37 of the 42 patients were women, that is 88.1 per cent as against 69.7 per cent in the gold-treated group and 59.1 per cent among the controls.

At the beginning of treatment the age of the men receiving combined therapy was on the average higher than in the gold-treated group or among the controls. The respective means are 54.8, 35.78, and 37.74 years. With respect to women the three groups displayed far lesser deviations, the mean age for those treated with hormones and gold being 33.3 years, for those given gold only 37.92 years, and for the controls 36.93 years.

The period from the onset of rheumatoid arthritis to the beginning of treatment averaged 3.77 years for men and 6.16 for women in the group receiving

combined therapy, 3.33 and 4.89 years in the gold-treated group, and 4.27 and 3.73 years respectively among the controls. On the whole, therefore, women given both hormones and gold would seem to have been ill longest.

Just as for the gold-treated patients and the controls, the joint status was estimated for each of the 42 patients undergoing hormone-gold therapy. The number of plus signs was thus found per patient and per affected joint. A detailed presentation will be found in the chapters on "Materials for Study" and "Immediate Results of Therapy". The analysis disclosed that the hormone-gold group had severer joint symptoms and signs than the other two groups at the beginning of treatment, as appears from the following figures.

		+ /person	+ /joint
Hormone-gold treated	men	18.2	1.7
	women	16.7	1.5
Gold-treated	men	8.61	1.32
	women	10.50	1.43
Controls	men	11.57	1.33
	women	11.51	1.26

The E.S.R. (1st hour), too, was higher at the beginning of treatment among those given hormones and gold than in either of the other groups. The mean for men was 90.8 mm and that for women 57.1 mm in the hormone-gold group, whereas the corresponding means for the gold-treated subjects were 28.8 and 35.3 and for the controls 24.1 and 29.9.

The period of observation—the interval from the beginning of treatment to the follow-up examination—for those undergoing the combined therapy was obviously much shorter than for the other two groups. Thus the average observation period was 1.36 for men and 1.26 for women in the gold-hormone group; and the corresponding figures for the gold-treated group and the controls were 6.25 and 6.40 and 7.65 and 7.93 respectively.

Clearly, therefore, the hormone-gold group differed from the others in several respects. It was composed mainly of women, and the 5 men it did contain were older than in the other groups. The women had on the whole been ill longer. The joint status and E.S.R. were much poorer, and the observation period was shorter throughout. These points must be taken into due account when the results are evaluated.

In most cases cortisone was the hormone used. The initial daily dosage was 200 to 300 mg given in divided doses. After a few days the total daily dosage was rapidly brought down to 150 or 75 mg, or less. In four cases (patients 2, 8, 28 and 40 in Table 61) ACTH was given subsequent to cortisone. ACTH alone was given to 5 patients (Nos. 33–37).

In 14 cases hormone therapy was given before gold and then discontinued. In 21 cases hormone therapy was commenced before gold treatment and con-

Table 61. Hormo

No.	Sex	Age years	Duration years	Joint status + per patient	Joint status + per joint	E.S.R.	Joint status + per patient	Joint status + per joint	E.S.R.	Immediate results	Follow-up years	Joint status + per patient	Joint status + per joint
				At beginning of treatment			At end of treatment					At follow-t	
1	F	36	10.76	23	2.1	62	22	2.0	54	unimproved	2.92		
2	F	32	5.64	29	1.8	55	24	1.5	29	slightly improved	1.01	24	1.5
3	F	34	6.82	14	1.3	103	14	1.3	112	unimproved	0.82	15	1.3
4	F	53	5.60	15	1.2	31	6	1.0	23	markedly improved	0.80	12	1.1
5	F	31	1.87	19	1.5	126	11	1.2	42	markedly improved	0.81	12	1.1
6	F	11	2.27	10	1.4	80	3	1.0	22	markedly improved	0.67	4	1.3
7	F	16	8.04	28	1.8	25	28	1.8	38	unimproved	1.93		
8	F	52	7.62	24	1.6	39	21	1.5	28	slightly improved	1.40	22	1.5
9	F	45	15.43	14	1.3	38	12	1.2	24	slightly improved	0.74	10	1.2
10	F	31	9.31	22	1.6	67	14	1.4	38	markedly improved	1.86		
11	F	39	12.48	17	1.6	36	14	1.3	40	unimproved	1.96		
12	M	55	3.28	10	2.0	81	10	1.7	91	unimproved	1.81		
13	M	51	0.93	22	1.6	120	22	1.6	52	slightly improved	1.82		
14	F	16	0.52	6	1.5	65	1	1.0	10	markedly improved	1.83		
15	F	44	7.85	20	1.3	35	20	1.3	85	worse	1.77		
16	F	35	3.96	18	1.5	28	14	1.2	30	slightly improved	1.45	16	1.3
17	F	28	9.50	20	1.4	26	15	1.2	18	slightly improved	1.72		
18	F	30	0.59	9	1.3	45	0	0	14	symptomless	0.64		
19	F	40	2.18	12	1.0	86	7	1.0	30	markedly improved	1.65		
20	F	39	0.80	12	1.5	89	2	1.0	23	markedly improved	1.65		
21	F	48	7.08	16	1.3	31	10	1.3	23	slightly improved	1.68		
22	F	24	1.45	13	1.7	93	13	1.2	68	unimproved	1.08	17	1.2
23	M	57	10.47	18	1.6	129	17	1.6	130	unimproved	1.62		
24	F	16	2.95	13	1.6	14	0	0	10	symptomless	1.59		
25	F	30	14.76	14	1.2	36	11	1.0	23	slightly improved	0.68	12	1.1
26	F	37	12.04	15	1.4	43	14	1.3	38	unimproved	1.24	14	1.3
27	F	16	6.10	20	1.7	80	20	1.6	25	slightly improved	1.12	12	1.2
28	F	42	1.06	15	1.3	38	13	1.3	53	unimproved	1.41	16	1.1
29	F	27	4.32	14	1.4	60	4	1.0	46	markedly improved	1.48		
30	F	39	7.66	16	1.2	29	12	1.0	22	slightly improved	1.07	15	1.3
31	F	33	12.03	13	1.3	44	5	1.0	15	markedly improved	1.47		
32	F	39	5.66	13	1.4	78	10	1.6	40	slightly improved	1.45		
33	F	42	3.15	21	1.4	55	20	1.4	40	unimproved	1.29		
34	F	8	5.34	20	1.5	88	18	1.4	57	slightly improved	0.97	22	1.4
35	F	35	11.81	18	1.5	106	12	1.2	98	slightly improved	1.17		
36	M	59	3.81	23	1.6	52	23	1.6	41	unimproved	1.14		
37	F	51	0.60	18	1.3	44	18	1.3	46	unimproved	0.94		

l treatment.

End results	Capacity of work	Severity of work	Hormone treatment C: cortisone or cortone. a: before; b: during; c: after gold treatment	Gold treatment Brands, total amount in g, No. injections
se	none		C 4450 a(+b)	Aurothion 6.5 (8)
ntly improved	none		C 1900 a(+b); ACTH 1720 b	Oleosanocrysin 2.1(11)
nproved	none		C 2770 a(+b)	Oleosanocrysin 2.7(11)
ntly improved	partial	light	C 3700 a(+b)	Aurodetoxin 5.5 (11)
ntly improved	partial	light	C 2055 a(+b)	Aurothion 9.5 (10)
kedly improved	full	light	C 3475 a(+b)	Aurothion 3.4 (10)
ntly improved	none		C 5015 a+b	Aurodetoxin 5.6 (11)
nproved	partial	light	C 5675 a+b; ACTH 320 b	Aurodetoxin 5.1 (11)
ntly improved	partial	light	C 4650 a(+b)	Aurothion 9.5 (10)
kedly improved	partial	light	C 4975 a+b	Aurothion 9.0 (10)
se	partial	light	C 390 b	Aurothion 6.3 (10)
ntly improved	partial	moderate	C 5550 a+b+c	Oleosanocrysin 0.9 (3)
nproved	none		C 4150 a	Oleosanocrysin 0.9 (4)
kedly improved	full	light	C 5050 a+b	Aurothion 1.5 (2)
se	none		C 8450 a+b+c	Aurodetoxin 0.6 (3)
nproved	partial	light	C 5500 a+b	Oleosanocrysin 2.7(10)
se	none		C 8125 a+b	Aurodetoxin 1.0(4) + Oleosanocrysin 1.8(7)
ptomless	full	moderate	C 5425 a+b	Aurodetoxin 0.3(2) + Oleosanocrysin 2.1(7)
kedly improved	partial	light	C 3000 a	Aurodetoxin 5.3 (10)
kedly improved	full	moderate	C 4350 a(+b)	Aurodetoxin 2.0(2) + Oleosanocrysin 1.8(7)
se	partial	light	C 4350 a+b+c	Aurothion 1.5 (2)
se	partial	light	C 9775 a	Aurothion 10.0 (10)
se	none		C 3775 c	Aurothion 5.0 (5)
ptomless	full	light	C 2950 a+b	Aurothion 1.0 (1)
nproved	partial	light	C 4375 a+b	Oleosanocrysin 2.7 (9)
nproved	none		C 3350 a(+b)	Oleosanocrysin 2.5(10)
kedly improved	none		C 2900 a(+b)	Aurothion 14.5 (16)
nproved	none		C 6300 a(+b); ACTH 160 b	Aurothion 7.5 (8)
kedly improved	partial	light	C 3700 a(+b)	Oleosanocrysin 2.9(10)
htly improved	none		C 3750 a	Oleosanocrysin 3.0(10)
kedly improved	partial	light	C 3700 a	Oleosanocrysin 0.9(6)
htly improved	partial	light	C 2200 a	Oleosanocrysin 2.7(9)
se	none		ACTH 250 b	Aurothion 2.0 (3) + Oleosanocrysin 1.5 (6)
se	none		ACTH 250 a	Oleosanocrysin 0.29(10)
htly improved	partial	light	ACTH 425 a	Aurothion 2.5 (3)
htly improved	partial	light	ACTH 200 a	Aurothion 11.0 (11)
htly improved	none		ACTH 510 b	Aurothion 8.0 (11)

Table

No.	Sex	Age years	Duratinn years	Joint status per patient (At beginning of treatment)	Joint status per joint (At beginning of treatment)	E.S.R. (At beginning of treatment)	Joint status per patient (At end of treatment)	Joint status per joint (At end of treatment)	E.S.R. (At end of treatment)	Immediate results	Follow-up years	Joint Status per patient (At follow-u	per joint (At follow-u
38	F	28	4.52	20	1.9	29	17	1.5	10	slightly improved	0.88		
39	F	18	8.79	18	1.3	60	13	1.1	11	markedly improved	0.54		
40	F	38	6.14	15	1.4	32	10	1.3	34	slightly improved	0.41		
41	F	49	1.11	13	1.3	117	9	1.1	15	markedly improved	0.45		
42	M	52	0.35	18	1.8	72	10	1.1	36	markedly improved	0.40		

tinued for some weeks or all of the latter. in 3 additional cases hormone therapy was continued for a period after the end of the gold course. All these patients received hormones for about 3 weeks preceding gold treatment. A patient received hormone therapy after undergoing gold treatment. This appears from the following tabulation where the record numbers shown in Table 61 are given in parentheses.

Hormones before gold	14 cases	(Nos. 13, 19, 22, 30–32, 34–36, 38–42)
Hormones before and with gold	21 cases	(Nos. 1–10, 14, 16–18, 20, 24–29)
Hormones before, with and after gold	3 cases	(Nos. 12, 15, 21)
Hormones with gold	3 cases	(Nos. 11, 33, 37)
Hormones after gold	1 case	(No. 23)

The gold drug was administered in the form of weekly injections, just as for the gold-treated patients described previously. Owing to severe reactions, usually accompanied by some degree of therapeutic improvement, some patients received a small number of injections only. Physical therapy was given too. The average duration of the combined treatment was 128 days.

In noting the immediate results of therapy the general fitness, blood status, etc. were, as before, taken into consideration; but the main points were post-therapeutic changes in joint status and E.S.R. These changes are also given in Table 61. The nomenclature is the same as before, i.e. symptomless, markedly improved, slightly improved, unimproved, and worse.

A glance at the table reveals that 2 of the 42 patients had become symptomless, 12 were markedly improved, 15 slightly improved, 12 unimproved, and the condition of one was aggravated. These facts are arranged in convenient form with the respective percentages and the record numbers from table 61 given in parentheses in the following tabulation.

t.

End results	Capacity of work	Severity of work	Hormone treatment C: cortisone of cortone a: before; b: during; c: after gold treatment	Gold treatment Brands, total amount in g, No. injections
tly improved	none		C 2300 a	Aurothion 5.5 (9)
kedly improved	full	light	C 2150 a	Aurothion 6.7 (9)
kedly improved	partial	light	C 675; ACTH 70 a	Aurothion 5.4 (10)
kedly improved	partial	light	C 1450 a	Aurothion 5.5 (5)
kedly improved	partial	heavy	C 1375 a	Aurothion 8.0 (8)

Immediate results of hormone-gold therapy

Symptomless . . .	2 cases,	4.7 %	(Nos. 18, 24)
Markedly improved	12 cases,	28.6 %	(Nos. 4–6, 10, 14, 19, 20, 29, 31, 39, 41, 42)
Slightly improved	15 cases,	35.7 %	(Nos. 2, 8, 9, 13, 16, 17, 21, 25, 27, 30, 32, 34, 35, 38, 40)
Unimproved . . .	12 cases,	28.6 %	(Nos. 1, 3, 7, 11, 12, 22, 23, 26, 28, 33, 36, 37)
Worse	1 case,	2.4 %	(No. 15)

Comparison of the E.S.R. level at the beginning and end of hormone-gold treatment reveals that it was practically unchanged in 7 cases (Nos. 11, 16, 23, 24, 35, 37, 40). In 5 cases (Nos. 3, 7, 12, 15, 28) it was higher and in the rest lower. The mean E.S.R. level at the beginning of treatment was 61.1 and at its end 40.1 mm.

Most of these patients were followed up by means of the same kind of questionnaires that were used for the gold-treated patients and the controls, the returned data on status and fitness for work being interpreted in the same way as before. The procedure is fully described in the chapters on materials for study and end results. In other words the condition at follow-up was compared with that at the beginning of treatment. It was feasible to examine 15 of the 42 patients personally when they were admitted to hospital for a new course of treatment. Joint status and E.S.R. have therefore been entered for these cases (Nos. 2–6, 8, 9, 16, 22, 25–28, 30, 34) in Table 61 together with the other follow-up results. Two of the patients gave their E.S.R. when answering the questionnaire (Nos. 18, 21). The average interval between the commencement of therapy and the follow-up examination was 1.27 years. The results secured are shown in the first tabulation overleaf.

Comparing the immediate results with the follow-up results, we find that 6 patients were somewhat better on the latter occasion. Two of those listed as slightly improved immediately after therapy had thus become markedly im-

End results

Symptomless	2 cases, 4.7 %	(Nos. 18, 24)
Markedly improved	12 cases, 28.6 %	(Nos. 6, 10, 14, 19, 20, 27, 29, 31, 39–42)
Slightly improved	12 cases, 28.6 %	(Nos. 2, 4, 5, 7, 9, 12, 30, 32, 35–38)
Unimproved	7 cases, 16.7 %	(Nos. 3, 8, 13, 16,25, 26, 28)
Worse	9 cases, 21.4 %	(Nos. 1, 11, 15, 17, 21–23, 33, 34)

proved at follow-up. Among those showing no change at first 4 were rated slightly improved at follow-up. This may be a manifestation of the delayed effect of gold which we have discussed in the foregoing. However, 14 patients showed aggravation at follow-up compared with the findings at completion of the course of therapy. Thus of those who initially were markedly improved 2 could later be considered slightly improved. Of those who were slightly improved 4 had become unimproved and 3 were aggravated at follow-up. Finally 5 of the cases regarded as unimproved after treatment showed aggravation on the later occasion. This suggests that the effects of therapy with hormones and gold combined have only a short duration.

The following scheme depicts the relationship between immediate and end results.

Immediate results	*End results*				
	Symptomless	Markedly improved	Slightly improved	Unimproved	Worse
Symptomless	2				
Markedly improved		10	2		
Slightly improved		2	6	4	3
Unimproved			4	3	5
Worse					1

The following degrees of fitness for work were found at the follow-up examination.

Able to do moderately heavy work	2 cases	(Nos. 18, 20)
Able to do light work	4 cases	(Nos. 6, 14, 24, 39)
Partially capable of doing heavy work	1 case	(No. 42)
Partially capable of doing moderately heavy work	1 case	(No. 12)
Partially capable of doing light work	18 cases	(Nos. 4, 5, 8–11, 16, 19, 21, 22, 25, 29, 31, 32, 35, 36, 40, 41)
Incapacitated	16 cases	(Nos. 1–3, 7, 13, 15, 17, 23, 26–28, 30, 33, 34, 37, 38)

When the end results are compared with the ability to work, it appears that those patients who were fully fit for work also were symptomless or markedly improved when followed up. The patient who was partially capable of doing heavy work was in addition considerably improved. The patient partially able to do moderately heavy work was slightly improved at follow-up. Among the 18 patients partially capable of doing light work 6 were markedly improved, 6

slightly improved, 3 unimproved and 3 aggravated. The 16 incapacitated patients included one who was rated markedly improved at follow-up; however, he still had marked joint changes. Furthermore, 5 of those incapacitated for work were slightly improved, 4 unimproved and 6 aggravated at follow-up. Hence we see that the degree of improvement and the ability to work were associated without being completely parallel.

An investigation of the relationship, if any, between therapeutic effect and the various combinations of hormones and gold used might yield interesting results. The point has been debated, as the review of literature shows. The following table reveals how the immediate and also the end results were distributed according to the various combinations of hormones and gold.

Immediate results	Hormone before gold	Hormone before and with gold	Hormone before, with and after gold	Hormone with gold	Hormone after gold
Symptomless	—	2	—	—	—
Markedly improved	5	7	—	—	—
Slightly improved	7	7	1	—	—
Unimproved	2	5	1	3	1
Worse	—	—	1	—	—
End results					
Symptomless	—	2	—	—	—
Markedly improved	6	6	—	—	—
Slightly improved	5	5	1	1	—
Unimproved	1	6	—	—	—
Worse	2	2	2	2	1

Naturally such figures warrant no very far-reaching conclusions. Most of the patients received hormone before, or before and during, gold therapy, and the results in these two classes appears more or less equivalent. In the groups not given hormone before gold the results were not so good, but all told there were only 4 such cases.

Another important point to remember in evaluating the results concerns changes in joint status, E.S.R., history of rheumatoid arthritis, age, etc. For this purpose the patients were divided into two equally large groups with respect to severity of joint symptoms at the beginning of therapy. The first comprised those with 6 to 16 + and the second those with 17 to 29 +. Thus, the immediate and end results in these groups appear as follows:

Immediate results	*Joint status*	
	6+–16+	17+–29+
Symptomless	2	—
Markedly improved	8	4
Slightly improved	6	9
Unimproved	5	7
Worse	—	1

End results	*Joint status*	
	6 + –16 +	17 + –29 +
Symptomless	2	—
Markedly improved . . .	8	4
Slightly improved	5	7
Unimproved	4	3
Worse	2	7

Judging by these figures the therapeutic effect is better when joint symptoms are mild. Of the 14 patients who were symptomless or markedly improved immediately after therapy, and of the 14 who were symptomless or markedly improved when followed up, 10 had joint symptoms in the 6 - to 16 – class prior to therapy. Of the 13 cases which were unchanged or aggravated after therapy 8 had been associated with severe joint symptoms between 17 – and 29 - : and of the 16 cases unimproved or aggravated at follow-up 10 had presented severe joint changes in such a class.

In the following tabulation the immediate and end results are related to the E.S.R. prior to treatment. The patients were divided into two classes. one comprising 22 subjects with E.S.R. under 60 and one with E.S.R. values of 60 or over.

Immediate results	Erythrocyte sedimentation rate	
	Under 60	60 or over
Symptomless	2	—
Markedly improved . . .	2	10
Slightly improved	10	5
Unimproved	7	5
Worse	1	—
End results		
Symptomless	2	—
Markedly improved . . .	2	10
Slightly improved	8	4
Unimproved	5	2
Worse	5	4

From these figures the conclusion might be drawn that patients with a higher E.S.R. responded better to this combination therapy than those with a lower E.S.R. The E.S.R. was 60 or over in 10 of the 14 patients who were symptomless or markedly improved immediately after therapy: and the same applies to the corresponding end results. On the other hand the E.S.R. was less than 60 in 8 of the 13 cases that were unimproved or aggravated by therapy. The same applies to 10 of the 16 cases which were found to be unimproved or aggravated at follow-up.

Among the subjects in this group 23 had been ill less than 6 years at the beginning of hormone-gold therapy, while the remaining 19 had been ill 6 years or

longer. Dividing the results in accordance with these two groups yields the following tabulation.

Immediate results	Years of illness	
	Under 6	6 or over
Symptomless	2	—
Markedly improved	9	3
Slightly improved	6	9
Unimproved	6	6
Worse	—	1
End results		
Symptomless	2	—
Markedly improved	7	5
Slightly improved	8	4
Unimproved	3	4
Worse	3	6

This reveals that 11 of the 14 cases which were symptomless or markedly improved at the end of therapy had been ill less than 6 years. Of the 14 symptomless or markedly improved cases at the follow-up examination 9 had set in less than 6 years before. Of the 13 patients who were unimproved or aggravated by therapy 7 had been ill 6 years or longer; and so had 10 of the 16 subjects who were unimproved or aggravated when followed up. These findings suggest that patients having a short history respond better to this therapy than those with a long history.

The relationship between the results and the patients' age at the beginning of treatment was studied by dividing them into two groups, one with 18 patients less than 35 years old and another with 24 who were 35 years or older.

Immediate results	Age in years	
	Under 35	35 or over
Symptomless	2	—
Markedly improved	7	5
Slightly improved	6	9
Unimproved	3	9
Worse	—	1
End results		
Symptomless	2	—
Markedly improved	7	5
Slightly improved	4	8
Unimproved	2	5
Worse	3	6

These figures suggest that better results were obtained in the young than in the old age group. Nine of the 14 subjects who were symptomless or markedly improved at the end of therapy were under 35. The same figures apply to the

follow-up examination. Of the 13 patients unimproved or aggravated at the end of therapy 10 were aged 35 years or more. And, lastly, of the 16 cases found unimproved or aggravated at the follow-up examination 11 occurred in patients who were 35 years or older.

Here it may be pointed out that 7 subjects were younger than 20 years at the beginning of treatment. One of these became symptomless and 3 others markedly improved following treatment. At follow-up the symptomless patient was still symptomless and 4 were considerably improved.

Comparison of the effects of combination treatment with those of gold treatment and of physical therapy is fraught with major difficulties owing to the disparity of the groups. As mentioned, the 42 patients undergoing hormone-gold therapy were in a far worse condition than the gold-treated subjects and the controls with respect to joint status, E.S.R. and duration of rheumatoid arthritis, etc. It should be mentioned here that as many as 27 of the 42 patients had previously been receiving gold therapy. 6 of them (Nos. 1, 3, 12, 21, 29, 32) one course, 9 (Nos. 4, 7, 9, 15, 25, 27, 33, 35, 39) 2 courses, and 12 (Nos. 2, 8, 10, 11, 16, 17, 26, 30, 31, 34, 38, 40) 3 or more courses. These gold courses were all administered a sufficiently long time prior to the hormone-gold treatment to make it highly unlikely that the effect of the latter in any way was influenced by the former. Nine of the 15 patients who had taken no gold course previously (60 per cent) were rendered symptomless or markedly improved by the hormone-gold therapy, whereas only 5 of the 27 who had been receiving gold did so (18.5 per cent). This clearly indicates that most of the cases were severe and intractable. Consequently it would seem most appropriate to draw any parallels between this group and that comprising subject who had undergone several courses of gold and physical therapy. While the latter cases were more severe than those receiving only one course, they were hardly as severe as those undergoing hormone-gold treatment. The immediate results for those with hormone-gold treatment and those with several courses of gold and physical therapy may be juxtaposed as follows:

Immediate results	After hormone-gold	After several gold courses	After several physical therapy courses
Symptomless and markedly improved, %	33.3	59.2	24.5
Slightly improved, %	35.7	24.8	37.4
Unimproved and worse, %	31.0	15.9	38.1

Apparently, therefore, the immediate results of hormone-gold therapy would seem to be inferior to gold and negligibly better than physical therapy. Analyzing the 27 hormone-gold patients who had received gold previously, we find that 18.5 per cent became symptomless or considerably improved, a proportion which appears lower even than that after physical therapy alone. Comparing the 15 hormone-gold treated patients without previous gold courses with gold-treated and control patients who had taken only a single course, we find that

symptomless or considerably improved patients constituted 60.0, 71.0, and 38.7 per cent respectively. Thus hormone-gold treatment seems inferior to gold alone in these cases also.

The following tabulation is a pendant to that above and includes the end results.

End results	After hormone-gold	After several gold courses	After several physical therapy courses
Symptomless and markedly improved, % .	33.3	42.0	30.1
Slightly improved, %	28.6	14.0	25.2

Thus the end results of hormone-gold therapy appear inferior to those of gold alone, but they are about the same as those of physical therapy. The fact that those given hormone-gold were observed for a much shorter time than the others obviously means that the end results in the different groups hardly can be compared even if they do provide some indication of the effect that hormone-gold treatment is inferior to gold alone.

Regrettably enough the available data for patients given hormone-gold therapy are too few and based on too short an observation period to warrant definite conclusions of a far-reaching nature. What can be said is that the results obtained suggest that combined therapy with hormones and gold is no better than and probably inferior to gold treatment alone.

COMBINED HORMONE-SALAZOPYRIN TREATMENT

As mentioned in the review of the literature, Professor N. Svartz of the Caroline Institute and the Caroline Hospital, Stockholm, has for a number of years used Salazopyrin (Azulfidine, salicylazosulfapyridine, 4-(Pyridil-2-amidosulfonyl)-3′-carboxy-4′-hydroxyazobenzene) in the treatment of rheumatoid arthritis, reporting favourable results even over longer periods when treating large series. Recently Professor Svartz has evolved a therapy for rheumatoid arthritis where Salazopyrin is given together with cortisone (or ACTH). She has now kindly consented to let me make therapeutic trials with this combination using the same mode of administration and dosage schedule as she originally employed.

From the beginning of February through October, 1953, the Svartzian mode of treatment was administered to 20 rheumatoid arthritis patients at the Pensions Board's Hospital, Nynäshamn. A chronological list of these patients is given in Table 62 which also gives each patient's sex, age and years of rheuma-

Table 62. Hormon

No.	Sex	Age years	Duration years	Joint status: + per patient (At beginning of treatment)	Joint status: + per joint (At beginning of treatment)	E.S.R. (At beginning of treatment)	Joint status: + per patient (At end of treatment)	Joint status: + per joint (At end of treatment)	E.S.R. (At end of treatment)	Interval from beginning of treatment to discharge, years	Joint status: + per patient (At discharge)	Joint status: + per joint (At discharge)	E.S.R. (At discharge)
1	F	52	0.96	14	1.2	53	5	1.6	30	0.13	3	1.5	29
2	F	48	12.80	15	1.9	60	10	1.4	21	0.18	8	1.1	27
3	F	40	3.56	18	1.5	52	15	1.9	15	0.17	15	1.9	41
4	M	58	0.82	11	1.2	27	1	1.0	6	0.12	1	1.0	6
5	M	59	9.70	19	1.6	37	12	1.2	30	0.13	12	1.2	25
6	M	53	6.70	18	1.3	76	18	1.3	36	0.19	14	1.2	45
7	F	58	5.70	7	1.8	37	5	1.2	22	0.20	5	1.2	37
8	M	49	4.51	30	1.9	70	25	1.6	55	0.23	25	1.6	54
9	F	56	4.97	12	1.2	75	6	1.0	35	0.16	4	1.0	47
10	F	45	5.28	10	1.3	31	4	1.0	12	0.13	4	1.0	12
11	F	38	0.91	16	1.3	32	10	1.2	18	0.14	10	1.2	16
12	F	54	7.55	10	1.3	36	6	1.2	15	0.09	5	1.2	25
13	F	35	0.86	9	1.5	30	5	1.3	8	0.11	4	1.0	8
14	F	46	1.94	14	1.4	46	9	1.1	35	0.22	6	1.0	34
15	M	49	2.28	20	1.4	56	14	1.2	40	0.21	16	1.1	31
16	F	49	3.91	13	1.3	55	5	1.2	8	0.13	5	1.2	37
17	F	51	4.20	10	1.0	22	6	1.0	12	0.11	3	1.0	15
18	M	51	1.21	8	1.1	26	5	1.1	29	0.08	5	1.1	16
19	M	19	1.30	8	1.3	27	4	1.0	12	0.08	4	1.0	9
20	F	55	2.89	10	1.4	43	6	1.2	17	0.13	7	1.4	28

toid arthritis at the beginning of treatment, joint status (number of plus signs per person and per affected joint) and E.S.R. (1st hour) at the beginning of treatment, joint status and E.S.R. at the end of treatment, years elapsed from beginning of treatment to discharge from hospital, joint status and E.S.R. at discharge, immediate results of therapy, years elapsed from beginning of treatment to follow-up study, joint status and E.S.R. at follow-up when available, and state of health and fitness for work when followed up.

While Table 62 provides a survey of the nature of the cases treated, it is of interest to study them in relation to the group of 502 gold-treated patients and to the control group of 362 subjects, just as was done for those cases given the combined hormone-gold treatment.

It appears that the sex distribution is much the same in the three groups. Thus 13 of the 20 hormone-Salazopyrin-treated patients were women, i.e. 65.0 per cent, and the corresponding percentages for the gold-treated group and the controls were 69.7 and 59.1 respectively.

The average age at the beginning of treatment, however, was quite a lot

azopyrin treatment.

Immediate results	Follow-up, years	Joint status: + per patient	Joint status: + per joint	E.S.R.	End results	Capacity of work	Severity of work
		At follow-up					
arkedly improved	0.29			22	markedly improved	full	light
arkedly improved	0.33			12	markedly improved	partial	light
ightly improved	0.32			27	slightly improved	full	light
arkedly improved	0.82	4	1.0	12	slightly improved	full	moderate
arkedly improved	0.32				markedly improved	partial	heavy
ightly improved	0.35				slightly improved	full	light
ightly improved	0.31			37	slightly improved	full	light
ightly improved	0.79	20	1.4	50	slightly improved	none	
arkedly improved	0.28				worse	partial	light
arkedly improved	0.21				markedly improved	partial	light
arkedly improved	0.30				slightly improved	partial	light
ightly improved	0.24				worse	partial	light
arkedly improved	0.26			9	markedly improved	full	light
arkedly improved	0.30				markedly improved	none	
ightly improved	0.69	20	1.4	56	unimproved	none	
arkedly improved	0.26			20	markedly improved	partial	light
arkedly improved	0.22			11	markedly improved	partial	light
ightly improved	0.47	5	1.2	12	slightly improved	full	heavy
arkedly improved	0.20				markedly improved	full	light
ightly improved	0.20			28	unimproved	partial	light

higher in this group than in the others. The mean age of men treated with hormone-Salazopyrin was 48.3 years and of women 48.2 years, versus 35.78 and 37.92 years for men and women in the gold-treated group and 37.74 and 36.93 years in the control group.

The average duration of rheumatoid arthritis from onset to beginning of treatment was 3.79 years for men and 4.27 years for women in this group, whereas the corresponding figures for the gold-treated group were 3.33 and 4.89 years and for the controls 4.27 and 3.73 years. In this respect, therefore, there was no appreciable difference between the three groups.

As previously explained for other groups, the joint status was evaluated in terms of the number of plus signs per person as well as per affected joint (cf. chapters on materials for study and immediate results of therapy). Comparing the joint status at the beginning of therapy in the hormone-Salazopyrin group with that in the gold-treated group and in the control group, we find that the first presented more plus signs per person, the means for men and women being 16.3 plus and 12.2 plus, 8.61 plus and 10.50 plus, and 11.57 plus and 11.51 plus,

respectively. But the average number of plus signs per joint proved to be about the same in the hormone-Salazopyrin group as in the gold-treated group, and slightly lower among the controls. Thus the mean plus number per joint was 1.4 for men and 1.4 for women in the hormone-Salazopyrin group, 1.32 for men and 1.43 for women in the gold-treated group, and 1.33 for men and 1.26 for women among the controls.

Considerably higher in the hormone-Salazopyrin cases than in the gold-treated cases or the controls, the E.S.R. means at the beginning of treatment in the respective groups were as follows: 45.6, 28.8 and 24.1 for men and 44.0, 35.3 and 29.9 for women.

The length of time from the beginning of treatment to the follow-up study was of necessity much shorter for those given hormone-Salazopyrin than for those given gold or for the controls. The mean duration of the observation period was thus merely 0.52 years for men and 0.27 years for women, which must be contrasted against 6.25 and 6.40 years for the gold-treated cases and 7.65 and 7.93 years for the controls.

Accordingly the group of 20 patients receiving hormone-Salazopyrin had a higher mean age than the gold-treated group and the controls, the joint symptoms were somewhat more severe, and the E.S.R. was considerably higher, but the observation period was much shorter. A comparison, if one at all can be made, between the results in these 20 cases and those in the other two groups must clearly take into account these deviations.

Medication with cortisone (and ACTH) and Salazopyrin combined was done in accordance with the following dosage schedule, as developed by Professor N. Svartz.

	Cortisone		*Salazopyrin*	
Day	Amount of dose	Doses given	Amount of dose	Doses given
1	25 mg (1 tab.)	4	0.25 g (½ tab.)	4
2	»	4	»	4
3	»	3	»	6
4	»	3	»	6
5	12.5 mg (½ tab.)	4	0.5 g (1 tab.)	4
6	»	4	»	4
7	»	3	»	6
8	»	3	»	»
9	»	2	»	»
10	»	»	»	»
11	»	»	»	»
12	»	»	»	»
13	»	»	»	»
14	»	»	»	»

	ACTH		*Salazopyrin*	
Day	Amount of dose	Doses given	Amount of dose	Doses given
15	10 I.U.	2	»	»
16	»	2	»	»
17	5 I.U.	3	»	»
18	»	2	»	»
19	»	1	»	»
20	Discontinued		»	»
21			»	»

The course thus spanned over three weeks during which, in addition, a certain amount of physical therapy was administered. After the end of the treatment as outlined above physical therapy was continued for a few weeks while the patient was still in hospital, and some patients continued to receive Salazopyrin. Varying from 28 to 84 days, the time elapsed from the beginning of hormone-Salazopyrin treatment to discharge from hospital averaged 53 days.

The joint status was assessed both immediately after the end of hormone-Salazopyrin therapy and at the time of discharge, the data labelled "immediate results" in Table 62 being those recorded at discharge from hospital, i.e. on an average 32 days after the end of the combined therapy.

The immediate results of therapy were recorded and are given in the same manner as used elsewhere in this paper. Attention was thus paid to general status, blood findings, etc., but mainly to the joint status and the E.S.R. The same terminology as used elsewhere was adopted, viz. symptomless, markedly improved, slightly improved, unimproved and worse.

It appeared that all of the 20 patients in this group responded favourably to treatment. Thus 12 patients (60 per cent) were markedly and 8 (40 per cent) slightly improved. This is shown in the following tabulation which includes the case record numbers extracted from Table 62.

Immediate results

Markedly improved . . . 12 cases, 60 % (Nos. 1, 2, 4, 5, 9–11, 13, 14, 16, 17, 19)
Slightly improved . . . . 8 cases, 40 % (Nos. 3, 6, 7, 8, 12, 15, 18, 20)

As compared with the beginning of treatment, the E.S.R. at discharge was unchanged in one case (No. 7), had declined 7 mm in one case (No. 17) and gone down more in the others. Thus the E.S.R. decrease lay between 10 and 19 mm in 11 cases (Nos. 3, 5, 8, 10–12, 14, 16, 18–20) and between 21 and 33 mm in the remaining cases. The average E.S.R. decrease was 17.5 mm.

An analysis of E.S.R. changes from the end of hormone-Salazopyrin therapy to discharge from hospital reveals that it had remained practically unchanged in 9 cases (Nos. 1, 4, 8, 10, 11, 13, 14, 17, 19), had declined a further small amount in 3 cases (Nos. 5, 15, 18), but gone up somewhat in the remaining 8 cases (Nos.

2, 3, 6, 7, 9, 12, 16, 20). For this reason the mean E.S.R. decline from the beginning to the end of hormone-Salazopyrin therapy was rather larger than the corresponding figure for the period from the beginning of treatment to discharge from hospital, viz. 21.8 as against 17.5 mm.

The joint status at discharge from hospital deviated negligibly from that immediately after hormone-Salazopyrin therapy. In two cases (Nos. 15, 20) the condition had become a bit worse, in 8 cases (Nos. 1, 2, 6, 9, 12–14, 17) it was slightly better, and in the remaining cases it remained unchanged. Consequently the results of hormone-Salazopyrin therapy would seem to have remained more or less stable through the weeks intervening between the end of therapy and discharge from hospital. Had cortisone or ACTH alone been given one might have expected a rapid turn for the worse.

Most of the patients in this group were followed up by means of the questionary mentioned previously. The information on state of health and fitness for work given therein was interpreted as for the other groups studied. (Cf. chapters on materials for study and end results.) Consequently the data recorded for the follow-up analysis applies to changes occurring from the beginning of treatment to the time of answering the questionary. Four of the patients (Nos. 4, 8, 15, 18) were followed up by the author personally when they were readmitted to hospital for renewed treatment. When replying to the questionary 8 patients gave figures for their E.S.R. (Nos. 1–3, 7, 13, 16, 17, 20). Averaging 0.36 years, the interval from the beginning of treatment and the follow-up analysis was at least 0.20 years and at most 0.82 years. The following end results were found.

End results

Markedly improved . . .	9 cases, 45 %	(Nos, 1, 2, 5, 10, 13, 14, 16, 17, 19)
Slightly improved	7 cases, 35 %	(Nos. 3, 4, 6–8, 11, 18)
Unimproved	2 cases, 10 %	(Nos. 15, 20)
Worse	2 cases, 10 %	(Nos. 9, 12)

It should be noted that the information contributed by the 2 patients given as aggravated was not such as to permit an accurate assessment of whether they were worse than at the beginning of hormone-Salazopyrin treatment. As will be shown, 9 of the 12 patients who were markedly improved at the end of treatment remained so at the follow-up analysis, so that 3 patients were not doing as well on the latter occasion as on the former. However, 2 of these subjects remained slightly improved and only 1 was included in the somewhat indefinite group of "aggravated" cases. Of the 8 cases showing slight improvement following therapy 5 were still slightly improved and 3 had become worse. Consequently 6 of the 20 patients were not as well at the follow-up analysis as they had been at the end of hormone-Salazopyrin therapy. As mentioned, however, the aggravation was rather doubtful in 2 of these cases.

It may be mentioned that among the 12 cases where information about the E.S.R. was available for the follow-up study 10 cases (Nos. 1–3, 7, 8, 13, 16–18, 20) showed unchanged or lower values than at discharge from hospital. The E.S.R. of one patient (No. 4) while slightly higher at follow-up than at the end of therapy was even so lower than at the beginning of treatment, and in another person (No. 15) it had risen to the original value.

The following tabulation shows the association between the immediate and the end results.

Immediate results	*End results*			
	Markedly improved	Slightly improved	Unimproved	Worse
Markedly improved . . .	9	2	—	1
Slightly improved	—	5	2	1

Fitness for work when followed up was as follows.

Able to do heavy work	1 case	(No. 18)
Able to do moderately heavy work . . .	1 case	(No. 4)
Able to do light work	6 cases	(Nos. 1, 3, 6, 7, 13, 19)
Partially capable of doing heavy work . .	1 case	(No. 5)
Partially capable of doing light work . .	8 cases	(Nos. 2, 9–12, 16, 17, 20)
Incapacitated	3 cases	(Nos. 8, 14, 15)

Among the 8 subjects fully capable of working 3 were markedly and 5 slightly improved at follow-up. The patient partially able to do heavy work was also markedly improved. Of the 8 patients partially able to do light work 4 were markedly improved, 1 slightly improved, 1 unimproved, and 2 worse when followed up. One of the 3 incapacitated for all work had improved markedly with respect to rheumatoid arthritis and her disability was primarily due to progressive arthrosis of the coxa. One of those unable to work showed slight improvement and the other was unchanged when followed up. The results of therapy evidently did not always agree with the ability to work; but, as pointed out in the chapter on fitness for work, the two things are not entirely governed by the same factors.

Obviously it is of interest to elucidate whether the results are associated with the nature of the cases in regard to joint status, E.S.R., history of rheumatoid arthritis, age, etc. The data were therefore analyzed with respect to each of these factors and divided into two groups, as done previously in connection with the results of hormone-gold therapy.

At the beginning of treatment half of the patients' joint status was such as to be designated 7 +–12 + and the other half 13 +–20 +. The results of treatment have in the below tabulation been arranged in accordance with this subdivision.

Immediate results	Joint status 7+–12+	13+–20+
Markedly improved . . .	6	6
Slightly improved	4	4
End results		
Markedly improved . . .	4	5
Slightly improved	3	4
Unimproved	1	1
Worse	2	—

Half the cases initially presented E.S.R. values under 40 mm and the other half values of 40 or more. Breaking down the results accordingly gives the following.

Immediate results	Erythrocyte sedimentation rate Under 40	40 and over
Markedly improved . . .	7	5
Slightly improved	3	5
End results		
Markedly improved . . .	5	4
Slightly improved	4	3
Unimproved	—	2
Worse	1	1

While 9 of the 20 patients had a history of rheumatoid arthritis shorter than 3 years, the remaining 11 had been ill 3 years or longer prior to their undergoing hormone-Salazopyrin therapy. Classified in accordance with this subdivision of the disease duration, the results are as follows.

Immediate results	Years of illness Under 3	3 or over
Markedly improved . . .	6	6
Slightly improved	3	5
End results		
Markedly improved . . .	4	5
Slightly improved	3	4
Unimproved	2	—
Worse		2

When the patients are classified by age at the beginning of this treatment, it appears that 10 were less than 50 years old and the others 50 or over. The results distributed accordingly are these:

Immediate results	Age in years	
	Under 50	50 or over
Markedly improved . . .	7	5
Slightly improved	3	5
End results		
Markedly improved . . .	6	3
Slightly improved	3	4
Unimproved	1	1
Worse	—	2

The groups of classified results in these 4 tabulations are evidently too small to warrant definite conclusions. Nevertheless there are no wide discrepancies between the various groups of joint status, E.S.R., history and age. This could be made in argument in favour of the contention that more or less the same therapeutic effect was obtained in cases with severe and mild joint symptoms, low and high E.S.R. values, short and long histories, and in young and old patients.

Additional light on the effect of combined hormone-Salazopyrin therapy may be had by considering individual cases in the series. The shortest histories occurred in cases 4 and 13, being 0.82 and 0.86 years respectively. At the beginning of treatment both patients displayed moderate joint symptoms evaluated as 11 − and 9 − per person. The E.S.R. was then 27 and 30 mm respectively. Both patients showed marked improvement following the hormone-Salazopyrin course. One of them (No. 4) proved slightly worse when followed up.

The longest histories occurred in cases 2 and 5 where onset had taken place respectively 12.80 and 9.70 years before hormone-Salazopyrin treatment was begun. The joint symptoms were more severe than in the two cases mentioned in the preceding paragraph, being recorded as 15 − and 19 − per patient; and the E.S.R. readings were higher, viz. 60 and 37. Both patients showed marked improvement immediately following therapy and had not become worse at follow-up.

Another appropriate example is the case with the most severe joint symptoms (No. 8). In this case the joint status corresponded to 30 −, and the E.S.R. was high, 70 mm. Onset had taken place about 4½ years before this treatment. Here the results were favourable. He improved slightly after hormone-Salazopyrin and was no worse at follow-up when the E.S.R. was 50. This indicates that severe cases of long duration may also respond favourably to this combined therapy.

In most cases, both mild and severe, the E.S.R., as mentioned, declined significantly.

Before any comparison can be made between this series, the gold-treated group and the controls with respect to therapeutic effect, every possible allowance must be made for the fact that these 20 cases, as mentioned, were more severe as reflected by joint status and E.S.R. Hence these cases should suitably

be compared with gold-treated patients and controls given more than one course of therapy. The latter cases were of course on the whole more severe than those receiving one course only but also probably a little more severe than those undergoing hormone-Salazopyrin treatment. In this connection it may be mentioned that 6 of the cases had previously been undergoing gold therapy, but in general one or more years before receiving this combined therapy. Of the 6 cases previously given gold 2 (Nos. 5, 17) had one course, 3 (Nos. 3, 6, 9) 2 courses, and one (No. 7) 3 courses. The immediate results of therapy are given below.

Immediate results	After hormone-Salazopyrin	After several gold courses	After several physical courses
Symptomless and markedly improved, %	60	59.2	24.5
Slightly improved, %	40	24.8	37.4
Unimproved and worse, %		15.9	38.1

Thus the immediate results of this combination therapy appear considerably superior to those obtained following physical therapy. Marked improvement seems to have taken place as often as among the gold-treated cases. The frequency of slight improvements seems somewhat higher, but, as mentioned, the patients given the combined treatment probably constituted cases slightly milder than the other patients.

We shall now consider the end results for those given hormone-Salazopyrin in relation to those for repeatedly gold-treated subjects and controls given several courses of physical therapy.

End results	After hormone-Salazopyrin	After several gold courses	After several physical courses
Symptomless and markedly improved, %	45	42.0	30.1
Slightly improved, %	35	14.0	25.2

It appears from the above that the end results for those given Salazopyrin combined with hormones were markedly better than the results for those undergoing several courses of physical therapy. The proportion of marked improvements among those given combined treatment and those given gold was approximately the same. A slightly higher percentage of slight improvements resulted among those undergoing combination therapy than among the gold-treated subject. However, here it should be recalled that the former cases probably were rather milder than the others and, moreover, that they were very few and observed for such a short time. Clearly, therefore, no definite conclusions should be drawn. Yet, even if nothing definite can be said about the possible significance of the Svartzian mode of treatment for rheumatoid arthritis, the results obtained must be considered quite favourable.

It is intended that the results of a follow-up study of these cases over a longer period shall be published on a later occasion.

A report on these trials with combination therapy was incorporated in the present work because the author felt he would benefit from forming his own opinion, based on personal experiences, on the question whether other topical forms of therapy are or might be superior to the gold therapy. As mentioned time and again, the patients given hormone-Salazopyrin treatment were much too few and they were observed for much too short a period, but these drawbacks notwithstanding the results have provided useful experiences of the value of combination therapy with hormones and chemotherapeutics in the treatment of rheumatoid arthritis, a therapy which currently is the subject of an animated debate.

THE RESULTS OBTAINED

While the present investigation was mainly designed to assess the effect of gold therapy in the treatment of rheumatoid arthritis, it also embraced trials of combined therapy with hormone-gold and hormone-Salazopyrin.

The available literature on gold treatment is first reviewed. It appears that many authors have obtained good results with gold therapy, but as some researchers have reported rather unfavourable findings no unanimity has been reached.

The effects of gold treatment were studied in a series of 502 patients, and another series of 362 subjects mainly given routine physical therapy was used for control purposes. The patients were followed up for varying lengths of time but in no case for less than 3 years after the beginning of the first course of treatment. The two series were for practical purposes equivalent in respect of age and sex distribution.

1. As a first step the immediate results of the first course of treatment were examined regardless of whether any patients received subsequent courses.

(*a*). The immediate results were much better among the gold-treated patients, the proportion of those who became symptomless being 5.3 ± 1.4 per cent higher and of those showing marked improvement 37.6 ± 3.2 per cent higher than among the controls. Classification of the patients according to sex disclosed no significant difference in the symptomless cases between those given gold and the controls, but there was a difference in marked improvement of 27.6 ± 5.4 per cent for men and 42.6 ± 3.8 per cent for women, which suggests that women showed greater improvement.

(*b*) The severity of the disease was assessed in terms of the E.S.R., the joint status and the length of history at the beginning of the first course of treatment. According to each of these factors the patients were divided into three groups. The effect of gold therapy compared with physical therapy appeared particularly good when the E.S.R. values were high. Furthermore those given gold displayed a higher reduction of the E.S.R. reading than the controls did after the first course of therapy. Gold therapy seemed superior to other therapy in cases with severe as well as of cases with mild joint status. Both among those with long histories and those with short histories gold therapy seemed to be more effective.

(*c*) The gold-treated cases and the control group were compared with one another with respect to E.S.R., joint status and history at the beginning of the

first course of treatment. It then appeared that those given gold had higher E.S.R. values, slightly less marked joint disability and longer histories than those not given gold. In this case the joint condition was recorded in terms of the total number of plus signs, representing symptoms from various joints, per person. Judging by the mean number of plus signs per affected joint, those given gold seemed to have slightly graver joint disorders. The gold-treated women had higher E.S.R. values, worse joint conditions and longer histories than the men given similar treatment. The same tendency was evident among the controls even if there were no particular differences. But the difference in the proportion of women between the two groups although significant was small and did not seem of any very great importance.

(*d*) When the figures for E.S.R., joint status (number of plus signs per person) and history were weighted so as to make the two groups fully comparable, the results for those given gold proved even more superior to those for the controls than the original figures had shown. Now the difference between gold-treated cases and controls for those who had become symptomless and those showing marked improvement regarded as one group was 45.6 ± 3.5 per cent.

2. The following can be said with regard to the therapy as such.

(*a*) The incidence of complications has previously been studied by SUNDELIN (1948) who put the mortality of gold-treated patients at 0.36 per cent. No observations of significance on this matter were made in the present investigation.

(*b*) Those given gold exhibited an excess mortality of 0.5 to 1 per cent. Two of the deaths in this group were probably due to the gold therapy, since the causes of death were thrombopenia and purpura and death occurred as soon as 0.2 and 0.5 years after the end of treatment. Besides, those who died in the gold-treated group were mostly severely ill persons.

(*c*) Gold salts of a variety of brands were used. Those given one course received an average of 8.3 injections together representing 0.64 g of elemental gold. Those given several courses received on average 9.5 injections amounting to 0.95 g of pure gold. The results were broken down according to the total amount of gold given. It appeared that small total amounts were about as effective as larger amounts. It should be noted, however, that those given little gold included a number of subjects whose severe reactions made it necessary to discontinue treatment and, indeed these cases seemed to benefit a little more from gold than the others.

3. A special analysis was made of subjects treated more than once.

(*a*) Among the gold-treated patients 68.7 per cent received one course and among the controls the same was true of 55 per cent. All the others underwent two or more courses. The figures thus tend to show that physical therapy courses oftener had to be repeated.

(*b*) If cases where treatment was repeated owing to aggravation were separated

from those where another course was given because the preceding one had unsatisfactory results, the E.S.R. changes taking place between courses suggested that the incidence of aggravation was higher among those given more than one course of gold therapy.

(*c*) Comparison of the E.S.R. values, joint status and history among those given one course and those given more than one course indicated that those given several courses were more serious cases at the beginning of the first course. This tendency was particularly prominent in the gold-treated group.

(*d*) The immediate results also tended to become successively less favourable as the number of courses increased, but gold treatment proved superior to physical therapy both for those given one course and those given more than one course.

(*e*) Furthermore, the response to gold treatment as well as to physical therapy was better when the preceding course had yielded unsatisfactory results than when aggravation had taken place. Among those given gold this finding was borne out by the E.S.R. values: cases where the E.S.R. level remained stationary or declined between courses responded better than cases where the E.S.R. level had increased.

(*f*) The weighted figures for the results of the last course (in terms of E.S.R. value, joint status and history) for all the gold-treated patients and all the controls showed that gold treatment was superior to physical therapy, although the superiority was not as great as after the first course. The difference between gold-treated patients and controls in regard to symptomless and markedly improved cases was now 38.3 ± 3.6 per cent (versus 45.6 ± 3.5 per cent after the first course).

(*g*) Examination of the E.S.R. changes from the beginning to the end of the treatment among those given one course and from the beginning of the first to the end of the last course among those given more than one course showed that the E.S.R. value declined much more in both the gold-treated groups than in the corresponding control groups.

4. The following can be deduced about the long-term results.

(*a*) Not less than 3 years after the beginning of the first course of treatment all the patients were asked to fill out a questionary, and on the basis of the replies an estimate was made of the condition of every patient who returned the form: this estimate was then compared with the condition at the beginning of the first course. Replies came in from about 95 per cent of the gold-treated patients and about 90 per cent of those given physical therapy. Obviously it would have been preferable if the writer had examined every patient himself, but mainly for economical reasons this was out of the question. The follow-up results thus obtained were better for those receiving gold salts than for those given physical therapy, but the difference was less marked than for the immediate results. For example, in the frequency of symptomless cases the two series

differed by 8.3 ± 2.1 per cent. and in the frequency of symptomless and markedly improved cases considered as one group they differed by 10.2 ± 3.4 per cent. In addition the gold-treated men had become symptomless significantly oftener than the men given physical therapy while both the symptomless and the markedly improved cases among gold-treated women showed a statistically probable preponderance over the corresponding groups of female controls.

(*b*) The follow-up results were analyzed along the same lines as the immediate results with respect to E.S.R. value, joint status and history at the beginning of the first course of treatment. It appeared that the follow-up results were better in the gold-treated series than in the controls, particularly for those with low E.S.R. values, those with mild joint disturbances and those with short histories.

(*c*) Just as for the immediate results, the follow-up results were weighted to remove the effect of discrepancies in E.S.R. values, joint status and history before the first course of gold treatment and physical therapy, but the outcome was much the same as that of the unweighted figures. Symptomless and markedly improved cases combined constituted a 17.2 ± 3.8 per cent higher proportion of the gold-treated patients than of the controls. It would seem to be of interest here to repeat the differences between the gold-treated series and the controls with respect to the total of symptomless and markedly improved cases, viz. (weighted figures)

after all first courses	45.6 ± 3.5%
after all last courses	38.3 ± 3.6%
at the follow-up study	17.2 ± 3.8%

(*d*) When the results immediately after the last course of treatment were compared with the follow-up findings, a number of those with initial improvement were found to show aggravation, the incidence of aggravation being significantly higher among the gold-treated patients. But on the other hand some of those who had not responded to therapy had subsequently undergone marked improvement. This was true for the gold-treated patients as well as for the controls. Delayed improvement tended to be a little more common among those given gold however, but the figures warrant no definite conclusions.

(*e*) Just as the immediate results, the follow-up findings tended to be less favourable with increasing number of courses. The late results after both one and several courses were better for those given gold than for the controls.

(*f*) The follow-up results were analyzed with respect to the time elapsed between the end of the last course and the follow-up study and also with respect to the interval from the beginning of the first course and the follow-up study. The latter was at least 3 and at most 11 years and it was on the whole somewhat longer for those not given gold. The intervals were also divided into classes and the late results compared between these classes within the therapeutic series, but no appreciable differences between the late results after varying intervals emerged.

5. The results were associated with the patients' age at the beginning of the first course of treatment. Then the immediate and late results of gold treatment in both young and old subjects proved better than those of physical therapy. On the whole gold treatment seemed to have equally good immediate results in young and old persons, whereas physical therapy tended to be slightly more effective in young persons. Both gold treatment and physical therapy seemed to have a better long-term prognosis in young persons than in old. The prognosis was comparatively favourable for persons aged 15 years or less when admitted to hospital for the first course of treatment (9 gold-treated subjects and 4 given physical therapy).

6. The working capacity was also considered at the follow-up study. Persons given gold and controls displayed no appreciable differences in working capacity. In this analysis due regard was paid to a number of factors such as nature of occupation, sex, follow-up results, age when followed up and existence of other diseases. Here it should be recalled that in some respects the cases treated with gold were more severe than those given physical therapy.

In order to obtain a more complete picture a search was made for those of the patients who had been awarded disablement pensions. The gold-treated series comprised approximately the same proportion of pensioned patients as the control series. However, among those whose working capacity was reduced or non-existent despite showing improvement when followed up, it appeared that a larger proportion of the gold-treated patients had been pensioned. This indicates that those improved gold-treated patients whose working capacity was reduced at the follow-up, had been more severely ill than the controls. It seems likely that this is at least one reason why, despite better follow-up results, the gold-treated patients had not a higher working capacity than the controls.

As shown previously a larger percentage of the gold-treated patients initially had higher E.S.R. values, severer joint disturbances (in terms of the mean number of plus signs per affected joint) and longer histories. Means for initial E.S.R., joint condition and length of history were therefore correlated with different grades of working capacity. Then particularly marked E.S.R. and joint condition differences emerged between the gold-treated series and the controls among those with reduced working capacity or none. Undoubtedly, therefore, gold-treated patients who were found to have little or no working capacity when followed up had been more severely ill initially than the corresponding controls.

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The present investigation also involved 42 patients with rheumatoid arthritis who were treated with combinations of hormones and gold and 20 similar patients who were treated with combinations of hormones and Salazopyrin, the whole being preceded by a brief survey of the relevant literature.

The 42 cases, 5 in men and 37 in women, treated with hormone combined with gold were on the whole severe. In comparison with the 502 gold-treated patients and the 362 subjects given physical therapy studied in the main part of the present investigation, they differed chiefly in having more severe joint disturbances, higher initial E.S.R. values and longer histories. The period of observation was much shorter (average: 1.27 years). Twenty-seven of them had previously received one or more courses of gold treatment. In most instances combination treatment took the shape of administration of cortisone (occasionally ACTH) for some weeks before the initiation of gold treatment and often continuing for the first weeks of the latter. In 3 cases hormone was given simultaneously with gold and in one case simultaneously with and for some time after gold treatment.

Immediately after treatment 2 cases (4.7 per cent) became symptomless, 12 cases (28.6 per cent) showed marked improvement, 15 cases (35.7 per cent) were slightly improved, 12 cases (28.6 per cent) were unchanged and one case (2.4 per cent) had aggravated.

At the follow-up examination—in 15 instances performed by the writer personally and in the others by questionnaire as for the gold-treated patients and the controls—2 of the cases were symptomless (4.7 per cent), 12 were markedly improved (28.6 per cent), 12 were slightly improved (28.6 per cent), 7 were unimproved (16.7 per cent), and 9 were aggravated (21.4 per cent).

In order to ascertain whether these results were associated with the character of the cases, i.e. with the joint status, E.S.R., history and age at the beginning of treatment, the patients were classified with respect to each of these factors into two approximately equal groups. It then appeared that both the immediate and the late results perhaps were somewhat better when the joint disturbances were mild, the E.S.R. value high, the history short and the age low.

In respect of the several combinations of hormone and gold which were used, fairly equivalent results were recorded for those given hormone before gold and for those given hormone before and concurrently with gold. The results seemed less favourable when hormone was administered concurrently with gold or concurrently with and after gold, but altogether there were only 4 such cases.

As the cases discussed here were far more severe than those receiving gold treatment or physical therapy, it is justified to compare them with the more severe cases of the latter type, i.e. those given more than one course of treatment, even though these were not as severe as those given hormone-gold. This procedure revealed that the immediate as well as the late results of combination therapy were inferior to those of gold treatment and negligibly better or about the same as the corresponding results of physical therapy.

Obviously the series of 42 patients treated with hormone-gold combinations was too small and the period of observation too short to warrant any far-reaching conclusions. Nevertheless the results suggest that combination treatment with hormone and gold in any case was not superior to treatment with gold alone.

The 20 patients with rheumatoid arthritis (7 men and 13 women) who were treated with a combination of hormone and Salazopyrin were slightly more ill than the 502 gold-treated and the 362 physically treated subjects dealt with in the main part of this investigation. Thus they had slightly more severe joint disturbances, higher initial E.S.R. values and somewhat higher ages. The observation period was much shorter, averaging 0.36 years. Six of them had previously undergone gold treatment. Combination therapy with hormone and Salazopyrin was conducted along the lines suggested by Professor N. Svartz, Stockholm.

Immediately after treatment 12 cases (60 per cent) were markedly and 8 (40 per cent) slightly improved.

At the follow-up examination—personally in 4 cases and by questionary in the rest—9 cases (45 per cent) were markedly improved. 7 cases (35 per cent) slightly improved, 2 cases (10 per cent) unimproved. and 2 cases (10 per cent) apparently aggravated.

In order to establish whether the therapeutic effect was related to the joint status, E.S.R., history and age at the beginning of treatment. the cases were classified according to each of these factors into two approximately equal groups. However, this disclosed no appreciable differences between the groups. and apparently all cases, even severe and with long histories. were capable of responding to this treatment.

As has been mentioned. these cases were more severe than those treated with gold alone and those given physical therapy. The most correct comparison would therefore seem to be with the more severe of the gold-treated subjects and of the controls, i.e. those given more than one course of treatment. The latter groups were, however, probably more severely ill than the cases given combination treatment. This analysis disclosed that the immediate as well as the late results of hormone-Salazopyrin treatment were better than the corresponding effects of physical therapy and approximately the same as or slightly better than those of gold treatment. Here it should of course be kept in mind that those given combination treatment probably were less severe cases and. in conjunction with the follow-up results. that the observation period was so very much shorter. However, it may be mentioned that the writer proposes to follow up these cases for an additional period.

While the 20 patients receiving combination treatment with hormone and Salazopyrin obviously were too few and the observation period too short to permit of definite conclusions concerning the value of this mode of treatment, the results obtained must none the less be considered favourable.

BIBLIOGRAPHY

Abrams, N. R. & Bauer, W.: "The treatment of rheumatoid arthritis with large doses of vitamin D", *J.A.M.A.*, 111:1632, 1938.

Adabache, D.: *La chrysotherapie des rhumatismes chroniques.* Thèse, Paris 1931.

Adams, C. H. & Cecil, R. L.: "Gold therapy in early rheumatoid arthritis", *Ann. Int. Med.*, 33: 163, 1950.

Alderin, K.: "Medicinsk-statistisk granskning av resultaten av 1927–28 års efterundersökning av kurortsfallen", Report to the Royal Pensions Board, 1928 (not published).

Annotations: "PABA and cortisone", *Lancet*, 261:674, 1951.

Bach, T. F.: "Gold treatment of the rheumatic diseases", *St. Barth. Hosp. J.*, 43:206, 1936.

—— *Arthritis and related conditions.* F. A. Davis Co., Philadelphia 1947.

Baggenstoss, A. H. & Rosenberg, E. F.: "Cardiac lesions associated with chronic infectious arthritis", *Arch. Int. Med.*, 67:241, 1941.

—— "Visceral lesions associated with chronic infectious (rheumatoid) arthritis", *Arch. Path.*, 35:503, 1943.

—— "Unusual cardiac lesions associated with chronic multiple rheumatoid arthritis", *Arch. Path.*, 37:54, 1944.

Barsi, I.: "A new treatment of rheumatoid arthritis", *Brit. M. J.*, 2:252, 1947.

Bauer, W.: in discussion on "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1063, 1939.

—— in discussion on "Treatment of rheumatoid arthritis with gold salt", *Tr. A. Am. Physicians*, 56:346, 1941.

Bauer, W., Clark, W. S., Ropes, M. W., & Kulka, J. P.: "Evaluation of hormone therapy in rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:305, 1952.

Bayles, T. B.: "Rheumatic heart disease in autopsied cases of rheumatoid arthritis", *Ann. Int. Med.*, 19:113, 1943.

Bayles, T. B., Colpoys, F. L., Fremont-Smith, P., Fergusen, B. C., & Paige, E.: "Significant remissions in rheumatic disease with high dosage cortisone therapy", *Ann. Rheumat. Dis.*, 10:476, 1951.

Bayles, T. B. & Hall, M. G.: "A yardstick for rheumatoid arthritis: Applied to patients receiving gold-salt therapy", *New England J. Med.*, 228:418, 1943.

Benett, G. A.: "Comparison of the pathology of rheumatic fever and rheumatoid arthritis", *Ann. Int. Med.*, 19:111, 1943.

Bilka, P. J.: "New developments in the use of cortisone in rheumatoid arthritis", *Minnesota Med.*, 34:1088, 1951.

Bille, B. S. V.: "Kronisk polyartrit hos barn och dess guldbehandling", *Nord. med.*, 37:308, 1948.

Bohman, F.: "Resultaten av Kungl. pensionsstyrelsens sjukvårdande verksamhet", *Social-Medicinsk Tidskrift*, 21:1, 1944.

Boland, E. W.: "The effects of cortisone and adrenocorticotropic hormone (ACTH) on certain rheumatic diseases", *California Med.*, 72:405, 1950.

—— "Prolonged uninterrupted cortisone therapy in rheumatoid arthritis", *Brit. M. J.*, 2:191, 1951.

—— "Rheumatoid arthritis: Experiences with hydrocortisone (free alcohol) and hydrocortisone acetate", *California Med.*, 77:1, 1952.

Boland, E. W & Headly, N E.: "Effects of cortisone acetate on rheumatoid arthritis", *J.A.M.A.*, 141:301, 1949.

— - "Management of rheumatoid arthritis with smaller (maintenance) doses of cortisone acetate", *J.A.M.A.*, 144:365, 1950.

- - "Results of long-continued cortisone administration in rheumatoid arthritis". *California Med.*, 74:416, 1951.

-- "Compound F used orally in patients with rheumatoid arthritis". *J.A.M.A.*. 148:981. 1952.

Boots, R. H.: "Gold therapy in rheumatoid arthritis", *J.A.M.A.*, 117:1560, 1941.

Bourderon, J.: *Contribution à l'étude du traitement des rhumatismes chroniques par les sels d'or.* Thèse, Paris 1934.

Brahme, L. & Andersson. H.: "Manganbehandling vid polyarthritis rheumatica". *Nord. med.*, 12:3501, 1941.

Browning, J. S., Rice, R. M., Lee, W. V., & Baker, L. M.: "Gold therapy in rheumatoid arthritis", *New England J. Med.*, 237:428, 1947.

Buckley, C. W.: "Prognosis in arthritis", *Lancet*, 230:1023, 1936.

Burbank, R. & Christensen. B. E.: "Specific vaccine treatment of one thousand cases of chronic arthritis with results and clinical observations", *J. Bone & Joint Surg.*, 29:246, 1931.

Cecil, R. L.: "Rheumatoid arthritis: A new method of approach to the disease", *J.A.M.A.*, 100:1220, 1933.

—— "The medical treatment of chronic arthritis", *J.A.M.A.*, 103:1583, 1934.

—— "The necessity of certain criteria for the diagnosis and cure of rheumatoid arthritis", *Ann. Int. Med.*, 11:637, 1937.

—— "Gold therapy in rheumatoid arthritis", *Proc. Interest. Postgrad. M. A. North America*, 1:253, 1940.

—— in conferences on therapy "Treatment of rheumatoid arthritis", *New York State J. Med.*, 41:689, 1941.

—— "Arthritis—a curable disease?", *J. Michigan M. Soc.*, 41:311, 1942.

Cecil, R. L. & Angevine, D. M.: "Clinical and experimental observations on focal infection with an analysis of 200 cases of rheumatoid arthritis", *Ann. Int. Med.*, 12:577, 1938.

Cecil, R. L. & Archer, B. H.: "Classification and treatment of chronic arthritis", *J.A.M.A.*, 87:741, 1926.

Cecil, R. L. & Kammerer, W. H.: "Rheumatoid arthritis in the aged", *Am. J. Med.*, 10:439, 1951.

Cecil, R. L., Kammerer, W. H., & de Prume, F. J.: "Treatment of rheumatoid arthritis with gold salts", *Tr. A. Am. Physicians*, 56:339, 1941.

Cecil, R. L., Nicholls, E. E., & Stainsby, W. J.: "The bacteriology of the blood and joints in chronic infectious arthritis", *Arch. Int. Med.*, 43:571, 1929.

Chase, J. D. & Lightbody, J. J.: "The use of massive-dose cortisone in the treatment of rheumatoid arthritis", *J. Michigan M. Soc.*, 51:1167, 1952.

Clark, W. S. & Bauer, W.: "Cardiac changes in rheumatoid arthritis". *Ann. Rheumat. Dis.*, 7:39, 1948.

Clark, W. S., Blais, J. A., & Tonning, H. O.: "Antirheumatic and metabolic effects of hydrocortisone in rheumatoid arthritis", *J. Clin. Investigation*, 31:621, 1952.

Cohen, A. & Dubbs, A. W.: "The treatment of rheumatoid arthritis with gold". *New England J. Med.*, 229:773, 1943.

Cohen, A., Dubbs, A. W., & Myers, A.: "The treatment of atrophic arthritis with estrogenic substance", *New England J. Med.*, 222:140, 1940.

Cohen, A., Goldman, J., & Dubbs, A. W.: "The treatment of rheumatoid arthritis with 417 courses of gold", *New England J. Med.*, 233:199, 1945.

Cohen, A. & McBride, T. J.: "Modern treatment of rheumatoid arthritis", *Pennsylvania M. J.*, 53:256, 1950

COLVER, T.: "The prognosis in rheumatoid arthritis in childhood". *Arch. Dis. Childhood*, 12:253, 1937.

COMROE, B. I.: in discussion on "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1064, 1939.

—— *Arthritis and allied conditions*. Lea & Febiger, Philadelphia 1944.

—— "The use and abuse of gold therapy in rheumatoid arthritis". *J.A.M.A.*, 128:848, 1945.

COPEMAN, W. S. C.: "Two cases of Still's disease cured by gold injections". *Proc. Roy. Soc. Med.*, 29:497, 1936.

—— *Treatment of rheumatism in general practice*. E. Arnold & Co., London 1946.

—— "Long-term treatment of rheumatoid arthritis", *Lancet*, 261:1165, 1951.

—— "Clinical use of cortisone", *Lancet*, 263:135, 1952.

COPEMAN, W. S. C., BISHOP, P. M. F., KELLIE, A. E., GLYN, J. H. H., SAVAGE, O., DODDS, E. C., STEWART, J. W., HENLY, A. A., & TWEED, J. M.: "Observations on prolonged cortisone administration in rheumatoid arthritis", *Brit. M. J.*, 1:397, 1952.

COPEMAN, W. S. & TEGNER, W.: "A review of gold therapy", *Lancet*, 232:554, 1937.

COSTE, F.: "Chrysotherapie des rhumatismes". *Rev. gén. de clin. et de thérap.*, 47:692, 1933.

COSTE, F., CAYLA, J., & DELBARRE, F.: "Association chryso-hormonale". *VIII congrès international des maladies rhumatismales*, I Rapports, Genève 1953.

COSTE, F. & FORESTIER, J.: "Valeur practique de la sedimentation globulaire au cours des rhumatismes chroniques", *Bull. et mém. Soc. méd. hôp. Paris*, 55:558, 1931.

COSTE, F. & LACAPÈRE, J.: "Cuti-vaccination du rhumatisme chronique". *Bull. et mém. Soc. méd. hôp. Paris*, 55:513, 1931.

CRAIN, D. C., KYLE, L. H., & RUBIN, M.: "The modern treatment of rheumatoid arthritis", *Postgrad. Med.*, 8:228, 1950.

CROSBY, G. J.: "The 'accidents' of gold treatment in rheumatoid arthritis", *Lancet*, 230:1463, 1936.

CROWE, H. W.: *Handbook of the vaccine treatment of chronic rheumatic diseases*. H. Milford, Oxford University Press, Oxford 1930.

—— "Chronic arthritis", *M. Press.*, 194:426, 1937.

—— "Chrysotherapy", *Lancet*, 233:990, 1937.

CURRIE, J. P.: "Treatment of rheumatoid arthritis with butazolidin", *Lancet*, 263:15, 1952.

CURRIE, J. P., PEEBLES BROWN, R. A., & WILL, G.: "Observations on the treatment of rheumatoid arthritis with butazolidin", *Ann. Rheumat. Dis.*, 12:88, 1953.

CYRIAX, J.: *Rheumatism and soft tissue injuries*. H. Hamilton, London 1947.

DAHLBERG, G.: *Statistical methods for medical and biological students*. G. Allen & Unwin Ltd, London 1940.

DAHLBERG, G., HAGLUND, G., & RICHTNÉR, N. G.: "The therapeutic significance of tonsillectomy in polyarthritis", *Acta Oto-Laryng.*, 38:306, 1950.

DAWSON, M. H.: in discussion on "Gold salt therapy in chronic arthritis". *J.A.M.A.*, 109:1308, 1937.

DAWSON, M. H. & BOOTS, R. H.: "Recent studies in rheumatoid (chronic infectious, atrophic) arthritis", *New England J. Med.*, 208:1030, 1933.

DAWSON, M. H., BOOTS, R. H., & TYSON, T. L.: "Gold salts in treatment of rheumatoid arthritis", *Tr. A. Am. Physicians*, 56:330, 1941.

DAWSON, M. H., SIA, R. H. P., & BOOTS, R. H.: "The sedimentation rate of the erythrocytes in chronic arthritis", *Proc. Soc. Exper. Biol. & Med.*, 27:657, 1930.

—— "The differential diagnosis of rheumatoid arthritis and osteoarthritis: The sedimentation reaction and its value", *J. Lab. & Clin. Med.*, 15:1065, 1930.

DOUTHWAITE, A. H.: "Gold treatment of rheumatoid arthritis", *Brit. J. Rheumat.*, 1:33, 1938.

—— "Treatment of rheumatoid arthritis with bismuth", *Brit. M. J.*, 2:276, 1944.

DRISCOLL, R. E. & MARKSON, D. E.: "One hundred cases of arthritis treated with a comparatively non-toxic gold compound", *Illinois M. J.*, 78:503, 1940.

Drukker, J. & Plaat: "Uitkomsten van behandeling met myochrysine", *Nederl. tijdschr. geneesk.*, 82:3629, 1938.

Edström, G.: "Die chronische rheumatische Infektarthritis des Kindes", *Ztschr. Rheumaforsch.*, 1:161, 1938.

— — "Några grundlinjer i den kroniska reumatiska infektartritens klinik och terapi", *Nord. med.*, 4:3596, 1939.

—— "Behandlingsresultat efter minst 5 års observation av kronisk polyartrit", *Nord. med.*, 5:421, 1940.

Egelius, N., Hävermark, N. G., & Nyström, G.: "Senresultat av guldbehandling vid reumatoid artrit", *Nord. med.*, 45:968, 1951.

—— "Late results of gold treatment in rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:17, 1952.

Ekelund, C.: "Late prognosis of rheumatoid arthritis", *Rev. españ. reum.*, 1951.

Ellman, P. & Lawrence, J. S.: "Gold therapy in rheumatoid arthritis: An assessment of its value with control experiments", *Reports on chronic rheumatic diseases*, No. 4, H. K. Lewis & Co., London 1938.

Ellman, P., Lawrence, J. S., & Thorold, G. P.: "Gold therapy in rheumatoid arthritis", *Brit. M. J.*, 2:314, 1940.

Engleman, E.: "Cortisone in collagen disease and other disorders", *Bull. Univ. Calif. Med. Center*, 11:12, 1950.

Ensign, D. C. & Sigler, J. W.: "Combination therapy in the treatment of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:306, 1952.

Fehlow, W.: "Goldbehandlung chronischer Polyarthritiden", *München. med. Wchnschr.*, 77: 2215, 1930.

—— "Behandlung chronischer auf dem Boden eines Dauerinfektes entstandener Gelenkerkrankungen", *Deutsche med. Wchnschr.*, 59:1206, 1933.

Feldt, A.: "Zur Chemotheraphie der Tuberkulose mit Gold", *Deutsche med. Wchnschr.*, 39:549, 1913.

—— "Chemotherapeutische Versuche mit Gold", *Klin. Wchnschr.*, 5:299, 1926.

Feldt, A. & Beckstroem, I.: "Die Goldbehandlung des chronischen Gelenkrheumatismus", *Ztschr. Rheumaforsch.*, 1:81, 1938; 2:93, 1939.

Feldt, A., Schoeller, W., Borgwardt, E., & Allardt, H.: "Der heutige Stand der Goldtherapie", *Med. Welt*, 4:437, 1930.

Fingerman, D. L. & Andrus, F. C.: "Visceral lesions associated with rheumatoid arthritis", *Ann. Rheumat. Dis.*, 3:168, 1943.

Fischer, F.: "ACTH and cortisone in treatment of rheumatoid arthritis: Preliminary report", *Ugesk. læger*, 114:879, 1952.

Fischer, F. & Broechner-Mortensen, K.: "Experiences with prolonged administration of ACTH and cortisone in rheumatoid arthritis", *VIII congrès international des maladies rhumatismales*, Summary of the communications, Genève, 1953.

Fletcher, E.: *Medical disorders of the locomotor system including the rheumatic diseases.* E. & S. Livingstone Ltd, Edinburgh 1947.

Fletcher, E. & Lewis-Faning, E.: "The chronic rheumatic diseases with special reference to chronic arthritis", *Post Grad. M. J.*, 21:1, 137, 176, 1945.

Forestier, J.: "L'aurotherapie dans les rhumatismes chroniques", *Bull. et mém. Soc. méd. hôp. Paris*, 53:323, 1929.

— "The treatment of rheumatoid arthritis with gold salts injections", *Lancet*, 222:441, 1932.

—— "Rheumatoid arthritis and its treatment by gold salts", *Lancet*, 227:646, 1934.

— "Rheumatoid arthritis and its treatment by gold salts: The results of six years experience", *J. Lab. & Clin. Med.*, 20:827, 1935.

— "Åtta års erfarenheter av guldterapi vid kronisk reumatism", *Nord. med. tidskr.*, 12:1414, 1936.

—— "La chrysothérapie en dehors de la tuberculose", *Progr. méd., Paris*, 66:902, 1938.

FORESTIER, J. & CERTONCINY, A.: "La chrysotherapie prolongée dans les polyarthrites", *Rev. rhum.*, 3:485, 1936.

—— "Le traitement des rhumatismes chroniques par les sels organiques de cuivre", *Presse méd.*, 64:884, 1946.

FRASER, T. N.: "Gold treatment in rheumatoid arthritis", *Ann. Rheumat. Dis.*, 4:71, 1945.

FREUND, R.: "Die Goldbehandlung der entzündlichen Gelenkerkrankungen", *Med. Klin.*, 27: 992, 1931.

FREYBERG, R. H.: "Recent trends in the treatment of rheumatoid arthritis", *Ohio State M. J.*, 38:813, 1942.

—— "Treatment of arthritis with vitamin and endocrine preparations", *J.A.M.A.*, 119:1165, 1942.

—— "Effects of cortisone and ACTH in rheumatoid arthritis", *Bull. New York Acad. Med.*, 26:206, 1950.

FREYBERG, R. H., BLOCK, W. D., & FROMER, M. F.: "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1063, 1939.

FREYBERG, R. H., BLOCK, W. D., & WELLS, G. S.: "Gold therapy for rheumatoid arthritis: Considerations based upon studies of the metabolism of gold", *Clinics*, 1:537, 1942.

FREYBERG, R. H., TRAEGER, C. T., ADAMS, C. H., KUSCU, T., WAINERDI, H., & BONOMO, I.: "Effectiveness of cortisone administered orally", *Science*, 112:429, 1950.

FREYBERG, R. H., TRAEGER, C. T., PATTERSON, M., SQUIRES, W., & ADAMS, C. H.: "Problems of prolonged cortisone treatment for rheumatoid arthritis – further experience", *Ann. Rheumat. Dis.*, 10:476, 1951.

FRONIUS, H.: "Die Behandlung des chronischen Gelenkrheumatismus mit Gold", *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 49:60, 1937.

FURLONG, J. J.: "The treatment of rheumatoid arthritis with gold salts", *Wisconsin M. J.*, 41: 910, 1942.

GARDNER, E. R.: "The use of gold in rheumatoid arthritis", *Med. Rec.*, 153:320, 1941.

GHRIST, D. G. & HENCH, P. S.: "The course and prognosis in chronic infectious arthritis: A study of relapses", *M. Clin. North America*, 13:1499, 1929.

GOLDIE, W.: "The effect of chrysotherapy on the sedimentation rate in rheumatoid arthritis", *Ann. Rheumat. Dis.*, 1:319, 1939.

GORDING, R.: "Kliniske og eksperimentelle undersokelser av led- og muskelreumatismus etiologi med særlig henblick paa den tonsillogene infektion", *Norsk mag. lægevidensk.*, 86:995, 1925.

GOSLINGS, J., HIJMANS, W., v. LIMPT, P. M., & v. GILSE, H. A.: "Prolonged treatment of rheumatoid arthritis with ACTH alone and with gold", *Brit. M. J.*, 2:1019, 1950.

GRABER-DUVERNAY, J.: "Betragtninger over Kemotherapien ved Behandlingen av den generelle progressive kroniske Rheumatisme", *Ugesk. læger*, 97:941, 1935.

GRAHAM, J. W. & FLETCHER, A. A.: "Gold therapy in rheumatoid arthritis", *Canad. M. A. J.*, 49:483, 1943.

GRIPWALL, E.: "Beiträge zur Aurodetoxinbehandlung der chronischen Infektarthritis", *Acta med. scandinav.*, 89:587, 1936.

GUÉNON, P. L.: *Essai de traitement des rhumatismes chroniques par les sels d'or insolubles en suspension huileuse.* Thèse, Marseille 1936.

HADEN, R. L.: "The treatment of rheumatoid arthritis", *Ohio State M. J.*, 33:257, 1937.

HALBERTSMA, T.: "Over goudbehandeling by chronische arthritis van kinderen", *Maandschr. kindergeneesk.*, 14:297, 1946.

HARTFALL, S. J. & GARLAND, H. G.: "Gold treatment of rheumatoid arthritis", *Lancet*, 229:8, 1935.

—— "Further observations on the gold treatment of rheumatoid arthritis", *Lancet*, 230:1459, 1936.

HARTFALL, S. J., GARLAND, H. G., & GOLDIE, W.: "Gold treatment of arthritis: A review of 900 cases", *Lancet*, 233:784, 838, 1937.

—— "Treatment of rheumatoid arthritis with a new gold salt", *Lancet*, 235:1410, 1938.

HARTUNG, E. J.: "The treatment of rheumatoid arthritis including gold salts therapy", *Bull. New York Acad. Med.*, 19:693, 1943.

HEILBORN, A.: "Die Solganalbehandlung septischer Erkrankungen", *Therap. Gegenw.*, 71:537, 1930.

HENCH, P. S.: "Gold salts for rheumatoid arthritis", *Ann. Int. Med.*, 26:618, 1947.

—— "The potential reversibility of rheumatoid arthritis", *Proc. Staff Meet., Mayo Clin.*, 24: 107, 1949.

—— "Effects of cortisone in the rheumatic diseases", *Lancet*, 259:483, 1950.

—— "Effects of the cortisones and corticotropins on rheumatic and articular diseases, especially rheumatoid arthritis", *VIII congrès international des maladies rhumatismales*, I. Rapports, Genève 1953.

HENCH, P. S., BAUER, W., CHRIST, D., HALL, F., HOLBROOK, W. P., KEY, J. A., & SLOCUMB, C. H.: "The present status of rheumatism and arthritis", *Ann. Int. Med.*, 11:1089, 1938.

HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H., & POLLEY, H. F.: "The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: 'Compound E') and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Preliminary report", *Proc. Staff Meet., Mayo Clin.*, 24:181, 1949.

—— "The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis", *Merck & Co.'s Annotated Bibliography*, Rahway, New Jersey, June 1950.

—— "Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions", *Arch. Int. Med.*, 85:545, 1950.

HENCH, P. S., OSGOOD, E. E., & WARNER, L. W.: "A synthesis of the diagnosis and treatment of the common 'rheumatic diseases'", *Army M. Bull.*, 60:1, 1942.

HENCH, P. S. & SLOCUMB, C. H.: "Results of local therapy for generalized arthritis, chronic infectious (atrophic) arthritis and other forms of rheumatism", *Proc. Staff Meet. Mayo Clin.*, 10:202, 1935.

HENCH, P. S., SLOCUMB, C. H., POLLEY, H. F., & KENDALL, E. C.: "Effects of cortisone and pituitary adrenocorticotropic hormone (ACTH) on rheumatic diseases", *J. A. M. A.*, 140:232, 1949.

HENDERSON, E., OSGOOD, J. W., WAGNER, M., MORRICK, F. J., & SENDS, H.: "Some preliminary observations on the treatment of rheumatoid arthritis with cortisone plus tocopherol", *J. Clin. Endocrinol.*, 10:800, 1950.

—— "Cortisone plus tocopherol in the palliative treatment of rheumatoid arthritis: A preliminary study", *J. Clin. Endocrinol.*, 11:170, 1951.

HENSCHEN, W.: *Ist Skorzonera ein "Gold-konzentrat der peripherie"*, Lucerne 1st. years 1941

HOGARTH, J. C.: "Butazolidine", *Lancet*, 263:779, 1952.

HOLMGREN, W. P.: "Evaluation of therapy in chronic atrophic arthritis", *Ann. Int. Med.*, 7:467, 1933.

HOLMGREN, H. P. & INGELMARK, B. E.: "Die physikalische Therapie bei rheumatischen Fibrarthritiden und Arthrosen", *Acta med. scandinav., Suppl.* 170, 1946.

HOLST, P.: "Über die Wirkung von Solganal bei Gelenkerkrankungen", *Deutsch. z. klin. Med.*, 181:485, 1932.

ISSAKOWA, S.: "Zur gemeinsamen Solganalbehandlung des chronischen Gelenkrheumatismus", *Deutsche med. Wchnschr.*, 57:1281, 1931.

JOSE, A.: *La pneumonie du rhumatisme chronique par les sels d'or*, These, Paris 1933.

JOSEPH, M.: "Über die kombinierte Polyarthritisbehandlung", *Dtsch. med. Wschr.*, 52:427, 555, 1926.

Jarløv, E. & Kragh, J.: "Die Bedeutung der Tonsillectomie bei chronischen Gelenkerkrankungen", *Acta med. scandinav.*, Suppl. 26, 1931.

Jonsson, E.: "Endokrinologi och reumatologi", *Nord. med.*, 44:1891, 1950.

—— "Hur bör den reumatoida artriten behandlas", *Nord. med.*, 50:1067, 1953.

Jonsson, E., Berglund, K., Ejrup, B., Göhle, O., & Friedman, C. E.: "Reumatiska hjärtförändringar vid kronisk polyartrit", *Nord. med.*, 41:73, 1949.

Jonsson, E., Berglund, K., Hävermark, N. G., Nyström, G., & Paulsen, F.: "Endokrinologiska synpunkter på vissa reumatiska och andra mesenkymala sjukdomstillstånd", *Svenska läk.-tidning*, 46:1921, 1949.

Jordan, E. P.: "Critical evaluation of vaccine therapy in rheumatism", *J.A.M.A.*, 109:1444, 1937.

Kahlmeter, G.: "Über die Bedeutung der Fåhreusschen Senkungsreaktion bei akuten und chronischen arthritiden", *Klin. Wchnschr.*, 5:889, 1926.

—— "Resultaten av vården vid pensionsstyrelsens kurorter för sjuka lidande av kronisk ledgångsreumatism", *Hygiea*, 89:514, 1927.

—— "The significance of serological and blood examinations in rheumatic disease", *Acta rheumatol.*, 3:33, 1929.

—— "X-ray therapy in chronic arthritis", *Reports on chronic rheumatic diseases*, No. 3:17, H. K. Lewis & Co. Ltd, London 1937.

Kalbak, K.: "Ambulatory sanocrysin treatment of patients suffering from chronic rheumatoid arthritis", *Ugesk. læger*, 107:595, 1945.

Kammerer, W. H.: in discussion on "Combination therapy in the treatment of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:307, 1952.

Kammerer, W. H. & Cecil, R. L.: "Cortisone in private practice", *VIII congrès international des maladies rhumatismales*, Summary of the communications, Genève 1953.

Kempf, W.: "Die Behandlung des chronischen Gelenkrheumatismus", *Ztschr. Rheumaforsch.*, 2:233, 1939.

Key, J. A.: in discussion on "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1063, 1939.

Key, J. A., Rosenfeld, H., & Tjoflat, O. E.: "Gold therapy in proliferative arthritis", *J. Bone & Joint Surg.*, 21:339, 1939.

Kling, D. H., Vento, J. P., & Sashin, D.: "Gold therapy in rheumatoid arthritis in the United States", *Rheumatism*, 5:93, 1949.

Kovacs, J.: "Vaccine therapy in chronic arthritis", *New York State J. Med.*, 36:316, 1936.

Kroner, J., Lintz, R. M., Tyndell, M., Andersen, L., & Nicholls, E. E.: "The treatment of rheumatoid arthritis with an injectable form of bee venom", *Ann. Int. Med.*, 11:1077, 1938.

Kuhns, J. G. & Joplin, R. J.: "Convalescent care in chronic arthritis", *New England J. Med.*, 215:268, 1936.

Kuipers, R. K. W.: *De goudbehandeling van het chronische gewrichtsrheuma.* Leiden 1939.

Kuzell, W. C. & Gardner, G. M.: "Salicylazo-sulfapyridine (Salazopyrin) in rheumatoid arthritis and experimental polyarthritis", *California Med.*, 73:476, 1950.

Landé, K.: "Die günstige Beeinflussung schleichender Dauerinfekte durch Solganal". *München. med. Wchnschr.*, 74:1132, 1927.

Lansbury, J.: "Gold therapy in arthritis", *Pennsylvania M. J.*, 47:216, 1943.

Lewy, F. H. & Freund, R.: "Die Behandlung des chronischen Infekts mit dem neuen Goldpreparat Solganal", *Deutsche med. Wchnschr.*, 44:1857, 1926.

Lillie, H. I. & Lyons, H. R.: "Tonsillectomy in myo-itis and arthritis", *J.A.M.A.*, 72:1214, 1919.

Logefeil, R. C. & Hoffman, R. A.: "Gold therapy in the treatment of arthritis", *Journal-Lancet*, 61:221, 1941.

Luft, R.: "Corticotropin och cortison", *Nord. med.*, 50:929, 1953.

McKenna, D. E.: in discussion on "Treatment of arthritis with particular reference to vaccines and allergic reactions", *New York State J. Med.* 36:1530, 1936.

Margolis, H. M.: in discussion on "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1064, 1939.

Margolis, H. M. & Caplan, P. S.: "Effects of pituitary adrenocorticotropic hormone (ACTH) in rheumatoid arthritis", *J.A.M.A.*, 145:382, 1951.

Mester, A.: "La chrysotherapie des polyarthrites chroniques", *Acta med. scandinav.*, 86:469, 1935.

Nicholls, E. E.: "Rheumatoid arthritis: Treatment with the sting of the honeybee", *New York State J. Med.*, 38:1218, 1938.

Norcross, B. M.: in discussion on "Evaluation of hormone therapy in rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:305, 1952.

Nyfeldt, A.: "Die Ebesal-Therapie der chronischen Infektarthritiden", *Ztschr. Rheumaforsch.*, 7:73, 1944.

Oka, M.: "Treatment of rheumatism", *J.A.M.A.*, 151:574, 1953.

L'Orange, V.: "Gullbehandling av kronisk polyarthritis", *Nord. med.*, 26:893, 1945.

Oren, H.: "Arthritis and its treatment with gold salts", *J. M. Soc. New Jersey*, 23:591, 1936.

de Pap, L.: "Le traitement combiné de la polyarthrite primitivement chronique", *Rev. rhum.*, 4:667, 1937.

Parr, L. J. A. & Shipton, E. A.: "Chrysotherapy in rheumatoid arthritis", *M. J. Australia*, 24:864, 1937.

Pemberton, R. L.: "One hundred cases of chronic arthritis treated by gold", *Lancet*, 128:1037, 1935.

Pemberton, R. L. & Peirce, E. G.: "A clinical and statistical study of chronic arthritis based on eleven hundred cases", *Am. J. M. Sc.*, 173:31, 1927.

Pemberton, R. & Robertson, J. W.: "Studies on arthritis in the army based on four hundred cases", *Arch. Int. Med.*, 25:231, 1920.

Phillips, R. T.: "The treatment of arthritis with gold salts", *New England J. Med.*, 214:114, 1936.

Pick, E.: "Versuche einer Goldbehandlung des Rheumatismus", *Wien. klin. Wchnschr.*, 40:1175, 1927.

Pilot, I.: in discussion on "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1064, 1939.

Polley, H. F. & Mason, H. L.: "Rheumatoid arthritis: Effects of certain steroids other than cortisone and of some adrenal cortex extracts", *J.A.M.A.*, 143:1474, 1950.

Price, A. E. & Leichtentritt, B.: "Gold therapy in rheumatoid arthritis", *Ann. Int. Med.*, 19:70, 1943.

Price, A. E., Reveno, W. S., Lightbody, J. J., vonder Heide, E. C., Kashtan, H. A., & Corrigan, K. E.: "Observations on the use of cortisone and corticotropin in rheumatoid arthritis", *J. Michigan M. Soc.*, 51:1183, 1952.

van Raalte, H. G. S.: "De uitkomsten der behandeling van rheumatoid arthritis met goudpraeparaten", *Nederl. tijdschr. geneesk.*, 82:3618, 1938.

Ragan, C.: "Rheumatoid arthritis", *Am. J. Med.*, 1:675, 1946.

Ragan, C., Demartini, F., Lamont-Havers, R., Jessar, R. A., Vaillancourt, de G., & Grokoest, A. W.: "A critical appraisal of current therapy in rheumatoid arthritis: With special reference to ACTH and cortisone", *Bull. New York Acad. Med.*, 28:493, 1952.

Ragan, C. & Tyson, T. L.: "Chrysotherapy in rheumatoid arthritis", *Am. J. Med.*, 1:252, 1946.

Ralston, R. J.: "Rheumatoid arthritis", *J.A.M.A.*, 149:1681, 1952.

Ravenna, P.: "A review of recent italien work on rheumatism", *Ann. Rheumat. Dis.*, 2:1, 1940.

Rawls, W. B., Gruskin, B. J., & Ressa, A. A.: "The value of colloidal sulphur in the treatment of chronic arthritis", *Am. J. M. Sc.*, 190:400, 1935.

Rawls, W. B., Gruskin, B. J., Ressa, A. A., Dworzan, H. J., & Schreiber, D.: "Analysis of results obtained with small doses of gold salts in the treatment of rheumatoid arthritis", *Am. J. M. Sc.*, 207:528, 1944.

Rawls, W. B., Gruskin, B. J., Ressa, A. A., & Jordon, M.: "The sedimentation rate and polymorphonuclear count in rheumatoid and mixed arthritis: Their value as an index to activity", *J. Lab. & Clin. Med.*, 19:830, 1934.

Ray, M. B.: "Note on the treatment of chronic arthritis with calcium aurothiomalate", *Practitioner*, 150:49, 1943.

Rinehart, J. F., Greenbery, L. D., Baker, F., Mettier, S. R., Bruckman, F., & Choy, F.: "Metabolism of vitamin C in rheumatoid arthritis", *Arch. Int. Med.*, 61:537, 1938.

Robinson, D.: "Gold therapy in rheumatoid arthritis", *Canad. M. A. J.*, 86:158, 1942.

Rohlin, S.: in discussion on "Reumatiska hjärtförändringar vid kronisk polyartrit", *Nord. med.*, 41:74, 1949.

Rohlin, S. & Sundelin, F.: "The heart in cases of rheumatoid arthritis", *Cardiologia*, 21:470, 1952.

Ropes, M. W. & Bauer, W.: "Rheumatoid arthritis: Its varied clinical manifestations", *New England J. Med.*, 233:592, 618, 1945.

Rosenbaum, E. E.: in discussion on "Combination therapy in the treatment of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:307, 1952.

Rosenberg, E. F.: "Rheumatoid arthritis: Experiences with cortisone (compound E), other adrenal cortical steroids and pituitary adrenocorticotropic hormone", *Indust. Med.*, 21: 67, 1952.

Rosenberg, E. F., Baggenstoss, A. H., & Hench, P. S.: "The cause of death in thirty cases of rheumatoid arthritis", *Ann. Int. Med.*, 19:114, 1943.

—— "The causes of death in thirty cases of rheumatoid arthritis", *Ann. Int. Med.*, 20:903, 1944.

Rosenberg, E. F., Bishop, L. F., Weintraub, H., & Hench, P. S.: "Cardiac lesions in rheumatoid arthritis", *Ann. Rheumat. Dis.*, 6:90, 1947.

—— "Cardiac lesions in rheumatoid arthritis", *Arch. Int. Med.*, 85:751, 1950.

Sashin, D. & Spanbock, J.: "Intravenous gold therapy in rheumatoid arthritis", *Med. Rec.*, 145:429, 1937.

Sashin, D., Spanbock, J., & Kling, D. H.: "Gold therapy in rheumatoid arthritis", *J. Bone & Joint Surg.*, 21:723, 1939.

Schnell, Å.: "The clinical features of rheumatic infections in the old", *Acta med. scandinav.*, 106:345, 1941.

Scholtz, H. G. & Schubert, D.: "Erfahrungen mit der peroralen Solganalbehandlung", *Ztschr. Rheumaforsch.*, 6:413, 1943.

Sclater, J. G.: "An analysis of 388 cases of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 3:195, 1943.

Secher, K.: "Behandling af Ledlidelser med Sanocrysin", *Ugesk. læger*, 94:1049, 1932.

—— "Die Behandlung von Gelenkleiden mit Sanocrysin", *Acta med. scandinav.*, 79:506, 1933(a).

—— "Behandlung von Gelenkleiden mit Sanocrysin", *Deutsche med. Wchnschr.*, 59:90, 1933(b).

—— "Behandling af Ledlidelser med Guldpræparater", *Nord. med. tidskr.*, 6:1388, 1933(c).

—— *Traitement des maladies rhumatismales par la Sanocrysin.* Copenhague 1933(d).

—— "Sanocrysinbehandlung bei medizinischen Gelenkleiden", *Der Balneologe*, 2:74, 1935(a).

—— "Yderligere Erfaringer angaaende Behandling av Ledlidelser med Sanocrysin", *Ugesk. læger*, 97:935, 1935(b).

—— "Sanocrysinbehandling af Ledlidelser med særligt Henblick paa Komplikationer ved Behandlingen", *Ugesk. læger*, 100:609, 1938.

—— *Directions for the treatment of rheumatic joint diseases with Sanocrysin and physical therapy.* A. F. Høst & Søn, Copenhagen 1946.

—— *The theoretical basis of the treatment of tuberculosis and polyarthritis with Sanocrysin: Own results of the polyarthritis treatment.* A. F. Høst & Søn, Copenhagen 1947.

Secher, K. & Gudiksen, E.: "Results from Sanocrysin therapy in non surgical joint diseases", *Acta med. scandinav.*, 86:370, 1935.

Senturia, B. D.: in discussion on "Sulphur metabolism and the effect of sulphur administration in rheumatoid arthritis", *J.A.M.A.*, 113:1063, 1939.

Short, C. L.: "Gold therapy of rheumatoid arthritis", *Bull. New England M. Center*, 4:31, 1942.

Short, C. L. & Bauer, W.: "Treatment of rheumatoid arthritis with fever induced by diathermy: A follow-up study", *J.A.M.A.*, 104:2165, 1935.

—— "The treatment of rheumatoid arthritis", *New England J. Med.*, 227:442, 1942.

—— "The course of rheumatoid arthritis in patients receiving simple medical and ortopedic measures", *New England J. Med.*, 238:142, 1948.

Short, C. L., Beckman, W. W., & Bauer, W.: "Gold therapy in rheumatoid arthritis", *New England, J. Med.*, 235:362, 1946.

Shulman, J.: "Butazolidone", *Lancet*, 263:887, 1952.

Sinclair, R. J. G. & Duthie, J. J. R.: "Salazopyrin in the treatment of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 8:226, 1949.

van der Sleen, I.: "Exposé des resultats acquis par la chrysotherapie atteints d'affections rhumatismales chroniques", *Gaz. méd. de France*, 44:939, 1937.

Slot, G.: "The therapeutic uses of gold", *Sind. M. J.*, 8:181, 1936.

Slot, G. & Deville, P. M.: "Treatment of arthritis and rheumatism with gold", *Lancet*, 226:73, 1934.

Smyth, C. J. & Freyberg, R. H.: "Experiences with gold salts in the treatment of rheumatoid arthritis", *Univ. Hosp. Bull., Ann Arbor*, 7:45, 1941.

Smyth, C. J., Freyberg, R. H., & Peck, W. S.: "Experiences with roentgen therapy in various rheumatic conditions", *J.A.M.A* , 115:2209, 1940.

Snorrason, E.: *Polyarthritis chronica primaria: Sanocrysinbehandling og Prognose.* V. Richter's Forlag, Kjøbenhavn 1950.

Snyder, R. G., Lust, F. J., Traeger, C., & Kelly, L.: "Gold salt therapy in chronic arthritis", *J.A.M.A.*, 109:1307, 1937.

Snyder, R. G. & Squires, W. H.: "Follow-up study of arthritic patients treated with activated vaporized sterol", *New York State J. Med.*, 41:2332, 1941.

Snyder, R. G. & Traeger, C.: "The present status of gold salt therapy in Europe and America in the treatment of chronic arthritis", *New York State J. Med.*, 43:245, 1943.

Snyder, R. G., Traeger, C. & Kelly, L.: "Gold therapy in arthritis: Observations on 100 cases treated with gold sodium thiosulphate and aurocein", *Ann. Int. Med.*, 12:1672, 1939.

Steinbrocker, O.: *Arthritis in modern practice.* W. B. Saunders Co., Philadelphia 1942.

—— "Therapeutic results in rheumatoid arthritis", *J.A.M.A.*, 131:189, 1946.

Steinbrocker, O., Berkowitz, S., Ehrlich, M., Elkind, M., & Carp, S.: "Phenylbutazone therapy of arthritis and other painful musculoskeletal disorders", *J.A.M.A.*, 150:1087, 1952.

Steinbrocker, O. & Blazer, A.: "A therapeutic score card for rheumatoid arthritis", *New England J. Med.*, 235:501, 1946.

Steinbrocker, O., McEachern, G. C., LaMotta, E. P., & Brooks, F.: "Experience with cobra venom in the arthralgias and related conditions", *J.A.M.A.*, 114:318, 1940.

Steinbrocker, O., Traeger, C. H., & Batterman, R. C.: "Therapeutic criteria in rheumatoid arthritis", *J.A.M.A.*, 140:659, 1949.

Stephens, C. A. L., Yeoman, E. E., Holbrook, W. P., Hill, D. F., & Goodin, W. L.: "Benefits and toxicity of phenylbutazone (Butazolidin) in rheumatoid arthritis", *J.A.M.A.*, 150:1084, 1952.

Stone, K.: *Diseases of the joints and rheumatism.* W. Heinemann, Ltd, London 1947.

Stone, R. E., Spies, T. E., & Niedermeier, W.: "Rheumatoid arthritis: Partial rehabilitation by interval therapy with ACTH and cortisone", *Lancet*, 259:555, 1950.

SUNDELIN, F.: "Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen", *Acta med. scandinav.*, Suppl. 117, 1941.
—— "Om sambandet mellan komplikationer och läkningstendens vid guldbehandling av kronisk polyarthrit", *Nord. med.*, 21:283, 1944.
—— "Guldbehandling vid kronisk polyartrit", *Nord. med.*, 37:303, 1948.
—— in discussion on "Reumatiska hjärtförändringar vid kronisk polyartrit", *Nord. med.*, 41: 74, 1949.
SUNDELIN, F. & ROHLIN, S.: "Frekvensen av ekg-förändringar vid kronisk polyartrit", *Nord. med.*, 47:328, 1952.
SWAIM, L. T.: in discussion on "Experiences with roentgen therapy in various rheumatic conditions", *J.A.M.A.*, 115:2209, 1940.
SVARTZ, N.: "Ett nytt sulfonamidpreparat: Förelöpande meddelande", *Nord. med.*, 9:554, 1941.
—— "Erfarenheter med salazopyrin", *Nord. med.*, 11:2261, 1941.
—— "Salazopyrin, a new sulfanilamide preparation", *Acta med. scandinav.*, 110:577, 1942.
—— "Fall av kronisk polyartrit behandlat med kombinerad kemoterapi och hypertermi", *Nord. med.*, 23:1525, 1944.
—— "Modern kemoterapi vid tarm- och ledaffektioner", *Nord. med.*, 23:1713, 1944.
—— "Kemoterapi vid rheumatisk polyarthrit", *Nord. med.*, 37:299, 1948.
—— "Behandling med periartikulära injektioner vid polyarthrit", *Nord. med.*, 39:1509, 1948.
—— "The treatment of rheumatic polyarthritis with acid azo compounds", *Rheumatism*, 4:180, 1948.
TALKOW, R. H. & BAUER, W.: "The failure of cobra venom to relieve pain in rheumatoid arthritis", *New England J. Med.*, 228:152, 1943.
TANBERG, A.: "Senkningsreaksionens forløp under badebehandling av den kroniske polyartritt", *Nord. med. tidskr.*, 13:648, 1937.
TARSY, J. M.: "Clinical experiences with gold salts in the treatment of rheumatoid arthritis", *New York State J. Med.*, 40:1185, 1940.
—— "Gold colloid and colloids of other heavy metals in the treatment of rheumatoid arthritis", *J. Lab. & Clin. Med.*, 26:1918, 1941.
TAYLOR, D.: "A table for the degree of involvement in chronic arthritis", *Canad. M.A.J.*, 36: 608, 1937.
TEGNER, W.: "The present trend of gold therapy for arthritis in Europe", *Proc. Staff Meet., Mayo Clin.*, 14:117, 1939.
THOMPSON, H. E.: in discussion on "Combination therapy in the treatment of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:307, 1952.
THOMPSON, H. E. & ROWE, H. J.: "Cortisone and gold therapy in chronic rheumatoid arthritis", *Ann. Int. Med.*, 36:992, 1952.
THOMPSON, H. E. & WYATT, B. L.: "Gold therapy in chronic atrophic arthritis", *Southwestern Med.*, 25:207, 1941.
THOMPSON, H. E., WYATT, B. L., & HICKS, R. A.: "Chronic atrophic arthritis", *Ann. Int. Med.*, 11:1792, 1938.
TOUW, J. F.: "De behandeling van primair chronische polyarthritis met goudpraeparaten", *Nederl. tijdschr. geneesk.*, 80:4302, 1936.
TRAEGER, C. H.: in discussion on "Combination therapy in the treatment of rheumatoid arthritis", *Ann. Rheumat. Dis.*, 11:306, 1952.
TRAUNER, L.: "Über die Rolle der organischen Goldsalze in der Therapie der rheumatischen Arthritiden", *Ztschr. Rheumaforsch.*, 5:288, 1942.
TRAUT, E. F. & BARTON, E. M.: "Gold therapy of arthritis", *Illinois M. J.*, 84:263, 1943.
UMBER, F.: "Zur Diagnostik und Therapie chronischer Gelenkerkrankungen", *Med. Welt*, 3:633, 1929.
UMBER, F., STÖRRING, F. K., & STÖTTER, E.: "Zur Goldbehandlung der Infektarthritiden und schleichende Infekte mit Aurodetoxin", *Therap. Gegenw.*, 76:456, 1935.

Waine, H., Baker, F., & Mettier, S. R.: "Controlled Evaluation of gold therapy in rheumatoid arthritis", *California Med.*, 66:295, 1947.

Wainwright, C. W. & Brown, T. M.: "The use of gold in the treatment of chronic rheumatoid arthritis", *Bull. Johns Hopkins Hosp.*, 69:578, 1941.

Ward, L. E., Polley, H. F., Slocumb, C. H., & Hench, P. S.: "Cortisone in treatment of rheumatoid arthritis", *J.A.M.A.*, 152:119, 1953.

Ward, E., Slocumb, C. H., Polley, H. F., Kendall, E. C., & Hench, P. S.: "Clinical effects of cortisone administered orally to 100 patients with rheumatoid arthritis", *Ann. Rheumat. Dis.*, 10:477, 1951.

Wetherby, M.: "Intravenous streptococcic vaccine treatment of chronic rheumatoid disease", *Ann. Int. Med.*, 14:1849, 1941.

Wiesel, L. L., Barritt, A. D., & Stumpe, W. M.: The synergistic action of para-aminobenzoic acid and cortisone in the treatment of rheumatoid arthritis", *Brooklyn Hosp. J.*, 8:148, 1950.

—— "The synergistic action of para-aminobenzoic acid and cortisone in the treatment of rheumatoid arthritis", *Am. J. M. Sc.*, 222:243, 1951.

Winkler, H.: "Gold therapy in rheumatoid arthritis", *North Carolina M.J.*, 4:161, 1943.

Woldenberg, S. C.: "Clinical evaluation of colloidal sulphur in the treatment of arthritis", *J. Bone & Joint Surg.*, 35:1003, 1937.

Wyatt, B. L., Hicks, R. A., & Thompson, H. E.: "Massive doses of vitamin D in the treatment of proliferative arthritis", *Ann. Int. Med.*, 10:534, 1936.

Young, D. & Schwedel, J. B.: "The heart in rheumatoid arthritis", *Am. Heart J.*, 28:1, 1944.

Zimmer, A.: *Die Behandlung der rheumatischen Krankheiten.* G. Thieme, Leipzig 1930.

CONTENTS